

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to CranMax® and reduction of the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract pursuant to Article 14 of Regulation (EC) No 1924/2006¹

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)^{2,3}

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ABSTRACT

Following an application from Jemo-pharm A/S, submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of Denmark, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to CranMax® and reduction of the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract. The food that is the subject of the claim is CranMax®. The Panel considers that the food, CranMax®, which is the subject of the claim is sufficiently characterised in relation to the claimed effect. The Panel considers that reduction of the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract is a beneficial physiological effect. One human study from which conclusions could be drawn for the scientific substantiation of the claim did not show an effect of CranMax® on reduction of the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract. The Panel concludes that a cause and effect relationship has not been established between the consumption of CranMax® and reduction of the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract.

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KEY WORDS

CranMax®, cranberry, *Vaccinium macrocarpon*, proanthocyanidins, urinary tract, health claims

¹ On request from the Competent Authority of Denmark following an application by Jemo-pharm A/S, Question No EFSA-Q-2013-00649, adopted on 10 April 2014.

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³ Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Marina Heinonen, Ambroise Martin, Hildegard Przyrembel, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren, Hans Verhagen and Peter Willatts for the preparatory work on this scientific.

Suggested citation: EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on the substantiation of a health claim related to CranMax® and reduction of the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract pursuant to Article 14 of Regulation (EC) No 1924/2006. EFSA Journal 2014;12(5):3657, 11 pp. doi:10.2903/j.efsa.2014.3657

Available online: www.efsa.europa.eu/efsajournal

SUMMARY

Following an application from Jemo-pharm A/S, submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of Denmark, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to CranMax® and reduction of the risk of urinary tract infection (UTI) by inhibiting the adhesion of certain bacteria in the urinary tract.

The scope of the application was proposed to fall under a health claim referring to disease risk reduction. The application includes a request for the protection of proprietary data.

The food that is the subject of the health claim is CranMax®, which contains cranberry (*Vaccinium macrocarpon*) powder obtained from the whole fruit and seeds. The product is marketed in the form of capsules. The applicant indicated that the product is standardised for proanthocyanidins (PAC) content. The Panel considers that the food, CranMax®, which is the subject of the health claim is sufficiently characterised in relation to the claimed effect.

The claimed effect proposed by the applicant is “prevents adhesion of *E. coli* to the uroepithelial cells in women, which is a risk factor for developing urinary tract infections (UTI)”. The target population proposed by the applicant is “women from 18 years complaining of recurrent UTI”. The Panel considers that the health claim refers to reduction of the risk of UTI by inhibiting the adhesion of certain bacteria in the urinary tract in healthy women without signs or symptoms of UTI and does not include the treatment of UTI. The Panel considers that reduction of the risk of UTI by inhibiting the adhesion of certain bacteria in the urinary tract is a beneficial physiological effect.

The applicant identified four human intervention studies, two *in vitro* studies and one review paper as pertinent to the claim.

The Panel considers that the one human study from which conclusions could be drawn for the scientific substantiation of the claim did not show an effect of CranMax® on reduction of the risk of UTI by inhibiting the adhesion of certain bacteria in the urinary tract.

Two *in vitro* studies and one narrative review paper addressed inhibition of adherence of *Escherichia coli* to the uroepithelial cells cultures in the presence of cranberry juice or PAC. The Panel considers that these studies do not provide evidence that inhibition of the adhesion of *E. coli* to uroepithelial cells demonstrated *in vitro* predicts the occurrence of a clinically relevant inhibition of the adhesion of certain bacteria to uroepithelial cells in humans.

The only human study from which conclusions could be drawn for the scientific substantiation of the claim did not show an effect of CranMax® on reduction of the risk of UTI by inhibiting the adhesion of certain bacteria in the urinary tract. On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of CranMax® and reduction of the risk of UTI by inhibiting the adhesion of certain bacteria in the urinary tract.

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BACKGROUND

Regulation (EC) No 1924/2006⁴ harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Articles 14 to 17 of this Regulation lay down provisions for the authorisation and subsequent inclusion of reduction of disease risk claims and claims referring to children's development and health in a Community list of permitted claims.

According to Article 15 of this Regulation, an application for authorisation shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA

- The application was received on 03/07/2013.
- The scope of the application was proposed to fall under a health claim referring to disease risk reduction.
- The scientific evaluation procedure started on 24/09/2013.
- On 22/11/2013, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application, and the clock was stopped on 04/12/2013, in compliance with Art. 18(3) of Regulation (EC) No 1924/2006.
- On 24/02/2014, EFSA received the requested information as submitted by the applicant and the clock was restarted.
- During its meeting on 10/04/2014, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to CranMax® and reduction of the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to CranMax® and reduction of the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of procyanidins in cranberry, a positive assessment of its safety, nor a decision on whether CranMax® is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

⁴ Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Jemo-pharm A/S, Hasselvej 1, 4780 Stege, Denmark.

Food as stated by the applicant

According to the applicant, the food for which this health claim is made is CranMax®—cranberry extract. One capsule contains 170–200 mg anthocyanins.

Health relationship as claimed by the applicant

According to the applicant, the claimed effect is the prevention of the adhesion of *E. coli* to uroepithelial cells, which is a risk factor for developing UTIs.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wordings for the health claim: “Prevent adhesion of *E. coli* to the uroepithelial cells in women which is a risk factor for developing urinary tract infections”.

Specific conditions of use as proposed by the applicant

The applicant has proposed an intake of 500–1000 mg per day of CranMax® cranberry extract. It can be administrated as 500 mg once a day or 250 mg twice a day or 500 mg twice a day. The target population proposed is women aged 18 years and over complaining of recurrent UTI.

ASSESSMENT

1. Characterisation of the food

The applicant stated that the food that is the subject of the health claim is CranMax®, which contains cranberry (*Vaccinium macrocarpon*) powder (500 mg) obtained from the whole fruit and seeds. The product is marketed in the form of capsules (capsule weight 623 mg).

The applicant indicated that the product is standardised for proanthocyanidins (PAC) content. PACs constitute a group of flavan-3-ols ranging from dimers to polymers. There are differences in the linkages (A- or B-type) between the monomeric units. The content of PACs in the product is measured by UV absorbance at 545 nm after acid hydrolysis and extraction in butanol. The PAC content is specified as $\geq 7.2\%$ (at least 36 mg in one capsule). The total phenols content of the product is also given.

Information about the manufacturing process (the cranberry pulp is dried and milled), the stability and the batch-to-batch variability was provided.

The Panel considers that the food, CranMax®, which is the subject of the health claim is sufficiently characterised in relation to the claimed effect.

2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is “prevents adhesion of *E. coli* to the uroepithelial cells in women which is a risk factor of developing urinary tract infections (UTI)”. The target population proposed by the applicant is “women from 18 years complaining from recurrent UTI”.

Bacterial adherence to mucosal surfaces is facilitated by fimbriae, which are proteinaceous fibres on the bacterial cell wall (Duguid et al., 1955; Beachey, 1981). Preventing adhesion facilitates urinary flushing of the bacteria, thereby preventing bacterial colonisation of the urinary tract (Foo et al., 2000).

The Panel considers that the health claim refers to reduction of the risk of UTI by inhibiting the adhesion of certain bacteria in the urinary tract in healthy women without signs or symptoms of UTI and does not include the treatment of UTI.

The Panel considers that reduction of the risk of UTI by inhibiting the adhesion of certain bacteria in the urinary tract is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

A Medline, Cochrane Library, EMBASE and Google engines were used in a literature search without language restrictions looking for clinical studies on CranMax® used for prevention of UTIs in women with recurrent UTIs. The decision tree used in the search process was not presented. The Panel notes that the search strategy was inadequately described.

The applicant identified four human intervention studies, two *in vitro* studies and one review paper as pertinent to the claim.

Stothers (2002) evaluated the effectiveness of CranMax® in the prevention of UTIs in women in a randomised, placebo-controlled, three-arm study. Subjects with at least two symptomatic UTIs in the prior calendar year, but currently free of UTI (150 women aged 21–72 years, mean 42 years), were randomised to ingest CranMax® 500 mg/day or cranberry juice (3 × 250 mL, containing the same amount of PACs), or placebo for 12 months (n = 50 subjects in each group). The endpoints measured were a 50 % decrease in symptomatic UTIs per year (UTI defined as the presence of symptoms and $\geq 10^5$ bacteria/mL in urine culture) and > 50 % decrease in annual antibiotic consumption. The cost-effectiveness of the use of cranberry products was also calculated as a primary outcome. A total of 127 women finished the study (40 subjects in the tablet group, 44 in the juice group and 43 in placebo group). The Panel notes that this publication reported insufficient information on the settings of the study, on the criteria used for UTI diagnosis, on the statistical methods applied and on the procedures used for urine analysis for scientific evaluation, and no clarification was provided by the applicant in response to a request by EFSA. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

Bohbot (2007) studied the effect of two cranberry products on the incidence of UTI in sexually active female subjects with recurrent urinary infections. In this randomised, double-blind, three-arm study, women who had had at least three episodes of UTI over the preceding six months and who had sexual intercourse on more than one occasion every two weeks were included. For 45 days following inclusion, the subjects were advised to take one capsule of either cranberry product with a brand name GynDelta® (claimed by the applicant as identical to CranMax®) or an extract of cranberry containing 36 mg of PAC A or a placebo within six hours after sexual intercourse. The number of recurring episodes of UTI, time to recurrence of UTI symptoms and product tolerability were evaluated as primary outcomes. Out of the 120 subjects entered into the trial, a total of 111 women (37 in each group) finished the study. The per protocol method was used in the statistical analysis of the results. The Panel notes that the diagnosis of UTI was based only on self-reported symptoms collected at the end of the study and it was not confirmed by urine analysis. The Panel also notes that there was no information on the management of the symptoms, in particular whether antibiotics were used, no information about the total amounts of the intervention product and placebo consumed over the entire study period in each group, and no clarification was provided by the applicant in response to an EFSA request for additional information. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

In a parallel, double-blind study, McMurdo et al. (2009) compared the effectiveness of PAC product (CranMax®) with low-dose trimethoprim (TMT) in the prevention of recurrent UTI in a population of women aged > 45 years with at least two episodes of antibiotic-treated UTIs or cystitis in the previous 12 months. Participants (n = 137) were randomised to receive either one capsule of CranMax®

(n = 69, mean age 62.6 ± 10.8 years) or 100 mg of TMT (n = 68, mean age 63.3 ± 10.1 years) taken at bedtime for six months. The primary endpoints were the recurrence rate of an antibiotic-treated UTI and the time to first recurrence. There were 17 (12 %) withdrawals from the study (six in the CranMax® group and 11 in TMT group). Statistical analysis was claimed to be intention to treat (ITT) analysis. The Panel notes that in reality the statistical analysis was conducted per protocol, as the comparison between groups did not take the missing data into account. The Panel also notes that the study was underpowered to detect differences between groups (*post hoc* power is much lower than specified in the methods; n = 168 per group should be randomised to reach power = 80 %). The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

In a similar study, Beerepoot et al. (2011) compared the effect of cranberry product (CranMax®) with trimethoprim–sulphamethoxazole (TMT-SMX) in the prevention of UTIs in premenopausal women with recurrent UTIs. The study was carried out in a group of women (n = 221) with a medical history of at least three self-reported symptomatic UTIs in the year preceding enrolment but free of symptoms at the time of enrolment. They were randomised to 12 months of ingestion of one tablet containing 480 mg TMT-SMX at night and one placebo capsule twice daily (n = 110, median age 36.1 years) or one CranMax® capsule twice daily and one placebo tablet at night (n = 111, median age 34.8 years). The primary outcomes were the mean number of symptomatic UTIs over 12 months, the proportion of patients with at least one symptomatic UTI, and the median time to the first symptomatic UTI. UTI was defined on the basis of a woman's subjective report of clinical symptoms, usually dysuria, frequency and/or urgency. Mean number of microbiologically confirmed UTIs, the percentage of patients with at least one recurrence and the median time to first microbiologically confirmed UTI constituted the secondary outcomes. A total of 110 participants (50 %) finished the study giving 53 who completed in the cranberry group and 57 in the TMT-SMX group. The statistical analysis was carried out to establish the non-inferiority of cranberry powder intake compared with TMT-SMX prophylaxis. Power calculation was performed accordingly. Analyses were completed by the use of inverse probability-of-censoring weighting, in order to correct for informative censoring. The mean number of clinical UTIs was 1.8 (95 % confidence interval (CI) 0.8–2.7) in the TMT-SMX group and 4.0 (95 % CI 2.3–5.6) in the cranberry group and the between-group difference after 12 months was outside the non-inferiority margin. The proportion of patients with at least one symptomatic UTI was higher in the CranMax® group (78.2 % vs. 71.1 %, p = 0.03) than in the control group. The median time to first recurrence was eight months for the TMT-SMX and four months for the cranberry group (p = 0.03). Secondary outcomes were not statistically different. The Panel notes that the number of drop-outs was large and no information was provided about handling of missing data, and that majority of comparisons were performed using inverse probability-of-censoring weighting, a technique which is likely to provide biased outcome estimates in the face of a small sample size and strong selection bias. The Panel notes that this study with several limitations showed that CranMax® was inferior to antibacterial therapy in the prevention of UTIs in premenopausal women with recurrent UTIs.

The applicant also submitted two *in vitro* studies and one review paper on the inhibition of adherence of *E. coli* to the culture of uroepithelial cells in the presence of cranberry juice or PAC (Zafriri et al., 1989; Howell et al., 1998; Lavigne et al., 2007). The Panel notes that several health claim applications on cranberry products standardised by their PAC content and in which inhibition of the adhesion of *E. coli* to uroepithelial cells by the urine of subjects consuming cranberry products was demonstrated, have already been evaluated by EFSA (EFSA, 2009; EFSA NDA Panel, 2011, 2013a, b). The studies provided in these applications did not establish that inhibition of the adhesion of *E. coli* to uroepithelial cells demonstrated *in vitro* or *ex vivo* predicts the occurrence of a clinically relevant inhibition of the adhesion of certain bacteria to uroepithelial cells in humans.

In weighing the evidence, the Panel considers that one human study from which conclusions could be drawn for the scientific substantiation of the claim did not show an effect of CranMax® on reduction of the risk of UTI by inhibiting the adhesion of certain bacteria in the urinary tract.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of CranMax® and reduction of the risk of UTI by inhibiting the adhesion of certain bacteria in the urinary tract.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food, CranMax®, which is the subject of the health claim is sufficiently characterised in relation to the claimed effect.
- The claimed effect is “prevention of adhesion of *E. coli* to uroepithelial cells which is a risk factor for developing urinary tract infections”. The target population as proposed by the applicant is healthy women complaining of recurrent UTI. Reduction of the risk of UTI by inhibiting the adhesion of certain bacteria in the urinary tract is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of CranMax® and reduction of the risk of UTI by inhibiting the adhesion of certain bacteria in the urinary tract.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on CranMax® and reduction of the risk of UTIs by inhibiting the adhesion of certain bacteria in the urinary tract pursuant to Article 14 of Regulation (EC) No 1924/2006 (Claim serial No: 0391_DK). July 2013. Submitted by Jemo-pharm A/S.

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ABBREVIATIONS

ITT	intention to treat
PAC	proanthocyanidin
TMT	trimethoprim
TMT-SMX	trimetophrim–sulphamethoxazole
UTI	urinary tract infection