

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to a Uroval[®] and urinary tract infection pursuant to Article 14 of Regulation (EC) No 1924/2006¹

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

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Valosun A.S. submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of the Czech Republic, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to cranberry extract and D-mannose contained in the food supplement Uroval[®] and urinary tract infections. The scope of the application was proposed to fall under a health claim referring to disease risk reduction. The Panel considers that the food, the cranberry extract and D-mannose containing food supplement Uroval[®], which is the subject of the health claim, is sufficiently characterised. The claimed effect is “prevent adhesion of bacteria to the cell surface, a risk factor for urinary tract infections.” The target population indicated by the applicant is those suffering from acute and / or chronic urinary infections. The Panel considers that reducing the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract is beneficial to human health. The Panel notes the poor quality of the references provided and that none of the references were related to a combination of a cranberry extract and D-mannose equivalent to Uroval[®]. The Panel considers that no scientific conclusion can be drawn from the references for the substantiation of the claim.

The Panel concludes that a cause and effect relationship has not been established between the consumption of the cranberry extract and D-mannose containing food supplement Uroval[®] and the reduction of the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract.

1 On request from Valosun A.S., Question No EFSA-Q-2009-00600, adopted on 04 December 2009.

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3 Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims for the preparation of this opinion: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren and Hans Verhagen.

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KEY WORDS

(Cranberry, proanthocyanidins, PAC, D-Mannose, bacterial adhesion, urinary tract infection)

SUMMARY

Following an application from Valosun A.S. submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of the Czech Republic, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to cranberry extract and D-mannose contained in the food supplement Uroval® and urinary tract infections. The scope of the application was proposed to fall under a health claim referring to disease risk reduction.

The food that is the subject of the health claim is the cranberry extract and D-mannose containing food supplement Uroval®. According to a conformity declaration, one tablet, coated with a polymer film agent, a hydroxyl-propylmethylcellulose, contains 300 mg of D(+)-mannose and 100 mg of cranberry extract with 10% proanthocyanidins. The Panel considers that the food, the cranberry extract and D-mannose containing food supplement Uroval®, which is the subject of the health claim, is sufficiently characterised.

The claimed effect is “prevent adhesion of bacteria (mostly *E. coli*) to the cell surface, a risk factor for urinary tract infections.” The target population indicated by the applicant is those suffering from acute and / or chronic urinary tract infections. The Panel notes that bacterial adherence precedes an infection and therefore inhibition of bacterial adhesion might result in a reduction for the risk of symptomatic urinary tract infections with bacteriuria $\geq 10^5$ cfu/mL. The Panel considers that reducing the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract is beneficial to human health.

The applicant identified eight references as being pertinent to the claim. The Panel notes the poor quality of the references provided and that none of the references were related to a combination of a cranberry extract and D-mannose equivalent to Uroval®. The Panel considers that no scientific conclusion can be drawn from the references for the substantiation of the claim.

The Panel concludes that a cause and effect relationship has not been established between the consumption of the cranberry extract and D-mannose containing food supplement Uroval® and the reduction of the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

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 that Regulation and are authorised in accordance with this Regulation and included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Articles 14 to 17 of that 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 that Regulation, an application for authorisation shall be submitted by the applicant to the national competent authority of a Member State, who will make the application and any supplementary information supplied by the applicant available to European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA:

- The application was received on 20/05/2009.
- The scope of the application was proposed to fall under a disease risk reduction claim.
- During the check for completeness⁵ of the application, the applicant was requested to provide missing information on 17/06/2009 and on 20/07/2009.
- The applicant provided the missing information on 07/07/2009 and on 27/08/2009.
- The scientific evaluation procedure started on 15/09/2009.
- During the meeting on 04/12/2009, the NDA Panel, after having evaluated the overall data submitted, adopted an opinion on the scientific substantiation of a health claim related to Uroval[®] and urinary tract infections.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16 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: Uroval[®] and urinary tract infection.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of Uroval[®], a positive assessment of its safety, nor a decision on whether Uroval[®] 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.

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 17 of Regulation (EC) No 1924/2006.

⁴ European Parliament and Council (2006). 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. Official Journal of the European Union OJ L 404, 30.12.2006. Corrigendum OJ L 12, 18.1.2007, p. 3–18.

⁵ In accordance with EFSA "Scientific and Technical guidance for the Preparation and Presentation of the Application for Authorisation of a Health Claim"

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Valosun A.S, Kytnerova 403/5, 62100 Brno, Czech Republic.

The application includes a request for the protection of proprietary data in accordance with Article 21 of Regulation (EC) No 1924/2006.

Food/constituent as stated by the applicant

The active ingredients containing in the food supplement Uroval[®] per daily dose:
D-mannose: 1200 mg
Cranberry extract: not less than 400 mg

Health relationship as claimed by the applicant

The bladder lining is comprised of polysaccharide molecules. Finger-like projections on the cell surface of *E. coli* bacteria adhere to these molecules, initiating an infection. In the presence of D-mannose, *E. coli* preferentially attach to D-mannose molecules forming a complex which is expelled with the next voiding. Cranberries (*Vaccinium macrocarpon*) prevent adhesion of bacteria (mostly *E. coli*) to the cell surface, a risk factor for urinary tract infections (UTI).

Wording of the health claim as proposed by the applicant

Cranberry extract and D-mannose, the main active ingredients of the food supplement Uroval[®], eliminate the adhesion of harmful bacteria to the bladder wall. The adhesion of harmful bacteria to the bladder wall is the main risk factor in the development of urinary tract infections.

Specific conditions of use as proposed by the applicant

The recommended daily dose contains minimally 1.2 g D-mannose and not less than 400 mg cranberry extract. The daily dose is used either once a day or is divided onto two doses and it is used twice a day, but always 20 minutes before a meal. The target population proposed by the applicant is those suffering from acute and / or chronic urinary infections.

ASSESSMENT

1. Characterisation of the food/constituent

The food that is the subject of the health claim is the cranberry extract and D-mannose containing food supplement Uroval[®]. According to a conformity declaration for “Uroval[®] manosa”, one tablet, coated with a polymer film agent, a hydroxyl-propylmethylcellulose, contains 300 mg of D(+)-mannose and 100 mg of “cranberry extract” with 10% proanthocyanidins, and the additives talc (5 mg), microcrystalline cellulose (90 mg) and magnesium stearate (5 mg). According to a certificate of analysis issued by the Chinese company Dalian Hongjiu Biotech Co Ltd., the botanical source of the ethanol/water- extracted cranberry powder is *Vaccinium macrocarpon L.*

D-mannose is a crystalline powder with the molecular formula of C₆H₁₂O₆ (Mw 180.16) and a CAS registry number of 3458-28-4. Analytical data on residual chloride, sulphate, and heavy metals as well as on microbial quality are given for two batches.

The applicant has provided a method of analysis for anthocyanidins assayed by UV-vis spectroscopy at wavelength of 550 nm.

The Panel considers that the food, the cranberry extract and D-mannose containing food supplement Uroval[®], which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect is “prevent adhesion of bacteria (mostly *E. coli*) to the cell surface, a risk factor for urinary tract infections.” The target population indicated by the applicant is those suffering from acute and / or chronic urinary infections.

Urinary tract infection (UTI) refers to the presence of bacteria in the urinary tract. Symptomatic UTIs are usually accompanied by bacteriuria at levels of $\geq 10^5$ /mL urine (WHO, 2006). Uropathogenic strains of *E. coli* bacteria cause up to 95% of UTIs (Ronald, 2003; WHO, 2006). Bacterial adherence to mucosal surfaces is generally considered to be an important prerequisite for colonisation and infection with bacteriuria (Harber and Asscher, 1985). Adherence is facilitated by fimbriae which are proteinaceous fibres on the bacterial cell wall (Beachey, 1981; Duguid et al., 1955). Preventing adhesion facilitates urinary flushing of the causative bacteria, preventing bacterial colonisation of the urinary tract (Foo et al., 2000). The Panel notes that bacterial adherence precedes an infection and therefore inhibition of bacterial adhesion might result in a reduction for the risk of symptomatic UTI with bacteriuria $\geq 10^5$ cfu/mL.

The Panel considers that reducing the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract is beneficial to human health.

3. Scientific substantiation of the claimed effect

The applicant identified eight references as being pertinent to the claim . No details concerning the search strategy have been provided.

One article published on a website of a consultant (Johnston, no date provided) claims cranberries, blueberries, and D-mannose to be alternatives to antibiotic treatment of UTI. Two references, published on a mannose producer’s website, reviewed the pharmacokinetics, safety and biological activity of dietary mannose (Gardiner, 2000; 2004). A booklet on a website claims D-mannose as being an alternative to antibiotics (Wright and Lenard, 2001). Another article published on a consultant’s website, summarises an uncontrolled clinical study on the effect of “two scoops of D-mannose” on 24 subjects with confirmed UTI and 18 subjects with painful-bladder-syndrome (Blue, no date provided). Another narrative review describes the anti-bacterial adhesion effect of cranberries and refers to clinical studies which have been conducted with products which considerably differed from Uroval[®] (Camesano et al., 2007). The Panel notes the poor quality of the references provided and that none of the references were related to a combination of a cranberry extract and D-mannose equivalent to Uroval[®]. The Panel considers that no scientific conclusion can be drawn from these six references for the substantiation of the claim.

A Cochrane review (Jepson and Craig, 2009) on cranberries and preventing UTI has been provided. The Panel notes that none of the studies referred to in this review concerns the combination of a cranberry extract and D-mannose equivalent to the food supplement Uroval[®], which is the subject of the claim. The Panel considers that no scientific conclusion can be drawn from this review for the substantiation of the claim.

The applicant provided an unpublished study summary on an uncontrolled human intervention trial (Motil, 2005) carried out with 56 patients (54 women, 2 men) with symptoms of uncomplicated acute infections in the low urinary tract and treated with “Uroval[®] manosa” for three months. The Panel

notes that the study summary does not provide sufficient details on the methodology used or on the study outcome. The Panel considers that no scientific conclusions can be drawn from this study for the substantiation of the claim.

In weighing the evidence, the Panel took into account the poor quality of the references provided and that none of the references were related to a combination of a cranberry extract and D-mannose equivalent to Uroval®.

The Panel concludes that a cause and effect relationship has not been established between the consumption of the cranberry extract and D-mannose containing food supplement Uroval® and the reduction of the risk of urinary tract infection 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, the cranberry extract and D-mannose containing food supplement Uroval®, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect is “prevent adhesion of bacteria (mostly E. coli) to the cell surface, a risk factor for urinary tract infections.” The Panel considers that reducing the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract is beneficial to human health.
- The Panel concludes that a cause and effect relationship has not been established between the consumption of the cranberry extract and D-mannose containing food supplement Uroval® and the reduction of the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on Uroval® and urinary tract infection pursuant to Article 14 of Regulation (EC) No 1924/2006 (Claim serial No: 0255_CZ). September 2009. Submitted by Valosun A.S.

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