



EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of a health claim related to Monurelle® and reduction of bacterial colonisation of the urinary tract by the inhibition of the adhesion of P-fimbriated E.coli to uroepithelial cells pursuant to Article 13(5) of Regulation (EC) No 1924/2006

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to Monurelle® and reduction of bacterial colonisation of the urinary tract by the inhibition of the adhesion of P-fimbriated *E.coli* to uroepithelial cells pursuant to Article 13(5) 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 Zambon B.V., submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of the Netherlands, 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 Monurelle® and reduction of bacterial colonisation of the urinary tract by the inhibition of the adhesion of P-fimbriated *E.coli* to uroepithelial cells. The food that is the subject of the health claim, Monurelle®, which is a combination of 120 mg cranberry (*Vaccinium macrocarpon*) extract (including 36 mg proanthocyanidins) and 60 mg of ascorbic acid, is sufficiently characterised. The claimed effect proposed by the applicant is reduction of *E.coli* adhesion to uroepithelial cells. The Panel considers that reduction of bacterial colonisation of the urinary tract by inhibition of the adhesion of P-fimbriated *E.coli* to uroepithelial cells is a beneficial physiological effect. Several health claim applications on cranberry products standardised by their proanthocyanidin content have already been evaluated by EFSA with an unfavourable outcome. The Panel notes that no studies from which conclusions could be drawn for the scientific substantiation of the claim were provided by the applicant. The Panel concludes that a cause and effect relationship has not been established between the consumption of Monurelle® and reduction of bacterial colonisation of the urinary tract by inhibition of the adhesion of P-fimbriated *E.coli* to uroepithelial cells.

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KEY WORDS

Monurelle®, proanthocyanidins, urinary tract, *E.coli* adhesion, *E.coli* colonisation, health claims.

¹ On request from the Competent Authority of the Netherlands following an application by Zambon B.V., Question No EFSA-Q-2012-00737, adopted on 24 January 2013.

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SUMMARY

Following an application from Zambon B.V. submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of the Netherlands, 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 Monurelle® and reduction of bacterial colonisation of the urinary tract by inhibition of the adhesion of P-fimbriated *E.coli* to uroepithelial cells.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.

The food that is the subject of the health claim, Monurelle®, which is a combination of 120 mg cranberry (*Vaccinium macrocarpon*) extract (including 36 mg proanthocyanidins) and 60 mg of ascorbic acid, is sufficiently characterised.

The claimed effect proposed by the applicant is “inhibition of the adhesion of the P-fimbriated *E. coli* bacteria to uroepithelial cells”. Upon a request by EFSA, the applicant clarified that the claimed effect does not refer to the reduction of urinary tract infections. Upon a request by EFSA, the applicant clarified that the target population is adult women. The Panel considers that reduction of bacterial colonisation of the urinary tract by inhibition of the adhesion of P-fimbriated *E.coli* to uroepithelial cells is a beneficial physiological effect.

The applicant provided only one *ex vivo* study with the substance complying with the specification of the food which is the subject of the claim. Other studies submitted included 13 *ex vivo* studies investigating the anti-adherence activity of human urine on uropathogenic *E.coli* strains following consumption of cranberry products other than Monurelle® product. Four *ex vivo* studies measuring antibacterial activity of human urine following consumption of cranberry products other than Monurelle® were also submitted. The applicant also referred to nine published opinions regarding cranberry products and urinary tract infections.

The Panel notes that several health claim applications on cranberry products standardised by their proanthocyanidin content have already been evaluated by EFSA. Although the *in vitro* anti-adherence effect of urine on uropathogenic *E. coli* strains following consumption of cranberry products was demonstrated in studies provided in these applications, such studies did not establish the validity of anti-adherence effects shown *in vitro* to predict the occurrence of a physiologically relevant bacterial anti-adherence effect within the urinary tract.

No human *in vivo* studies from which conclusions could be drawn for the scientific substantiation of the claim were provided by the applicant.

A randomized, double-blind, placebo-controlled cross-over study (Tempera et al., 2010) was designed to evaluate the *ex vivo* inhibitory activity of urine samples from female volunteers (aged 18-65 years) after one week’s consumption of Monurelle® on the adhesiveness of two strains of *E.coli* to uroepithelial human cells. Two groups of 12 female volunteers each were enrolled, one group with negative history and one group with positive history of recurrent cystitis. Adhesion tests were performed using HT1376 human bladder carcinoma cells. Urine samples from participants were incubated together with *E.coli* strains and thereafter put in contact with the uroepithelial cells. The adhesion index was determined by counting the average number of bacteria per cell as determined by examining 100 cells, with each test repeated three times.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of Monurelle® and reduction of bacterial colonisation of the urinary tract by inhibition of the adhesion of P-fimbriated *E.coli* to uroepithelial cells.

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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, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) 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 23/06/2012.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.
- On 09/08/2012, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
- On 11/09/2012, EFSA received the missing information as submitted by the applicant.
- The scientific evaluation procedure started on 28/09/2012.
- On 25/10/2012, 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. The clock was stopped on 30/10/2012 and restarted on 14/11/2012, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- On 14/11/2012, EFSA received the requested information (which was made available to EFSA in electronic format on 13/11/2012).
- During its meeting on 24/01/2013, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to Monurelle® and reduction of bacterial colonisation of the urinary tract by inhibition of the adhesion of P-fimbriated *E.coli* to uroepithelial cells.

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 Monurelle® and reduction of bacterial colonisation of the urinary tract by inhibition of the adhesion of P-fimbriated *E.coli* to uroepithelial cells.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of Monurelle®, a positive assessment of its safety, nor a decision on whether Monurelle® 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: Zambon B.V., Basicweg 14b 3821 BR Amersfoort, the Netherlands.

Food/constituent as stated by the applicant

According to the applicant, the food for which this health claim is made is Monurelle®, a food supplement constituted of 120 mg cranberry (*Vaccinium macrocarpon*) extracts (including 36 mg proanthocyanidins) and 60 mg ascorbic acid.

Health relationship as claimed by the applicant

According to the applicant, the claimed effect is the inhibition of the adhesion of P-fimbriated *E. coli* bacteria to uroepithelial cells. Without adhesion *Escherichia coli* cannot infect the mucosal surface of the urinary tract. The general anti-adhesion properties of cranberry were discovered over 20 years ago, challenging the original belief that the acidity of fruit was responsible for the antibacterial effect.

Upon a request by EFSA, the applicant clarified that the claimed effect does not refer to the reduction of urinary tract infections, and that the target population is adult women.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wordings for the health claim: "Proanthocyanidins from Monurelle® may help to support defence against bacterial pathogens in the lower urinary tract"; "Proanthocyanidins from Monurelle® cranberry product may help to reduce the P-fimbriated *E. coli* adhesion to uroepithelial cells"; "The *in vitro* and *ex vivo* studies conducted with Monurelle® or with urine from subjects who consumed Monurelle® show an inhibition of the adhesion of the P-fimbriated *E. coli* bacteria to uroepithelial cells".

Specific conditions of use as proposed by the applicant

The applicant has proposed an intake of one tablet per day of Monurelle® supplying 36 mg/day of proanthocyanidins. The target population proposed is adult women.

ASSESSMENT

1. Characterisation of the food/constituent

Upon a request by EFSA, the applicant stated that the food that is the subject of the health claim is the Monurelle® product that is a combination of 120 mg cranberry (*Vaccinium macrocarpon*) extract (including 36 mg proanthocyanidins) and 60 mg of ascorbic acid.

The proanthocyanidins (PAC) constitute a group of flavan-3-ols ranging from dimers to polymers. The monomeric flavan-3-ols (catechin and epicatechin) are not considered PACs. There are differences in the linkages (A- or B-type) between the monomeric units. The cranberry extract is standardised to 30% proanthocyanidins expressed as procyanidin C1 in chromatographic (HPLC) analysis. The product also contains ascorbic acid (vitamin C). Data on batch-to-batch variability were given. The stability of the product is established for six months.

The Panel considers that the food product, Monurelle®, a combination of proanthocyanidins from cranberries and ascorbic acid, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect is "inhibition of the adhesion of P-fimbriated *E. coli* bacteria to uroepithelial cells". Upon a request by EFSA, the applicant clarified that the claimed effect does not refer to the reduction of urinary tract infections, and that the target population is adult women.

Bacterial adherence to mucosal surfaces 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 bacteria, thereby preventing bacterial colonisation of the urinary tract (Foo et al., 2000).

The Panel considers that reduction of bacterial colonisation of the urinary tract by inhibition of the adhesion of P-fimbriated *E.coli* to uroepithelial cells is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

A Medline/Pubmed database was used in literature search with the following key words: (i) *Vaccinium macrocarpon*, cranberry, canneberge, (ii) proanthocyanidins, (iii) vitamin C, ascorbic acid, (iv) *Escherichia coli*, urinary tract infection, uropathogens. In addition, companies involved with the distribution of *Vaccinium macrocarpon* preparations were asked to provide information about both published and unpublished trials. A manual search of review articles was also performed.

The applicant provided only one *ex vivo* study with the substance complying with the specification of the food which is the subject of the claim. Other studies submitted included 13 *ex vivo* studies investigating the anti-adherence activity of human urine following consumption of cranberry products other than the Monurelle® product on uropathogenic *E.coli* strains. Four *ex vivo* studies measuring antibacterial activity of human urine following the consumption of cranberry products other than Monurelle® were also submitted. The applicant also referred to nine published opinions regarding cranberry products and urinary tract infections (five opinions of the AFSSA/ANSES, one recommendation of the AFSSAPS, and three opinions of EFSA).

The Panel notes that several health claim applications on cranberry products standardised by their PAC content have been evaluated already by EFSA (EFSA 2009; EFSA 2011). Although the *in vitro* anti-adherence effect of urine on uropathogenic *E. coli* strains following consumption of cranberry products was demonstrated, such studies did not establish the validity of anti-adherence effects shown *in vitro* to predict the occurrence of a physiologically relevant bacterial anti-adherence effect within the urinary tract.

No human *in vivo* studies from which conclusions could be drawn for the scientific substantiation of the claim were provided by the applicant.

A randomized, double-blind, placebo-controlled cross-over study (Tempera et al., 2010) with the product complying with the specification (as described in Section 1 above) was designed to evaluate the *ex vivo* inhibitory activity of urine samples from female volunteers (aged 18-65 years) after one week consumption of Monurelle® on the adhesiveness of two strains of *E.coli* to uroepithelial human cells. Two groups of 12 female volunteers each were enrolled, one group with negative history and one group with positive history of recurrent cystitis. Adhesion tests were performed using HT1376 human bladder carcinoma cells. Urine samples from participants were incubated together with *E.coli* strains, and thereafter put in contact with the uroepithelial cells. The adhesion index was determined by counting the average number of bacteria per cell as determined by examining 100 cells with each test repeated three times. The Panel considers that no evidence was provided to show that this *in vitro* study can predict the occurrence of a physiologically relevant bacterial anti-adherence effect within the human urinary tract.

The Panel concludes that a cause and effect relationship has not been established between the consumption of Monurelle® and reduction of bacterial colonisation of the urinary tract by inhibition of the adhesion of P-fimbriated *E.coli* to uroepithelial cells.

CONCLUSIONS

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

- The food product, Monurelle®, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect is “help to reduce the P-fimbriated *E. coli* adhesion to uroepithelial cells”. The target population as proposed by the applicant is adult women. Reduction of bacterial colonisation of the urinary tract by inhibition of the adhesion of P-fimbriated *E.coli* to uroepithelial cells is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of Monurelle® and reduction of bacterial colonisation of the urinary tract by inhibition of the adhesion of P-fimbriated *E.coli* to uroepithelial cells.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on Monurelle® pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0362_NL). July 2012. Submitted by Zambon B.V.

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GLOSSARY AND ABBREVIATIONS

AFSSAPS	Agence Francaise de Sécurité Sanitaire des Produits de Santé
ANSES	Agence Nationale de Sécurité Sanitaire de l'Alimentation
HPLC	high performance liquid chromatography
PAC	proanthocyanidins
UTI	urinary tract infection