SCIENTIFIC OPINION

ADOPTED: 6 July 2021

doi: 10.2903/j.efsa.2021.6776

MegaNatural®-BP grape seed extract and maintenance of normal blood pressure: evaluation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006

EFSA Panel on Nutrition, Novel Foods and Food allergens (NDA)

Abstract

Following an application from Praline i Čokolada j.d.o.o. submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 *via* the Competent Authority of Croatia, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to MegaNatural®-BP grape seed extract and maintenance of normal blood pressure. The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. MegaNatural®-BP, a grape seed extract standardised for total phenolics, gallic acid and the catechin and epicatechin content, is sufficiently characterised. The proposed claimed effect, maintenance of normal blood pressure (BP), is a beneficial physiological effect. Among the two human intervention studies provided from which conclusions could be drawn, one showed an effect of MegaNatural®-BP (300 mg/day) on BP in adults with normal and high normal BP when consumed daily for 6 weeks, whereas the second study did not show an effect of MegaNatural®-BP at the same daily dose consumed for 8 weeks in adults with normal and high normal blood pressure or stage 1 hypertension. The evidence provided did not establish a plausible mechanism by which the food could exert the claimed effect *in vivo* in humans. The evidence provided is insufficient to establish a cause and effect relationship between the consumption of MegaNatural®-BP and maintenance of normal blood pressure.

Keywords: MegaNatural®-BP, grape seed extract, blood pressure, health claim

Requestor: Competent Authority of Croatia following an application by Praline i Čokolada j.d.o.o.

Question number: EFSA-Q-2020-00718

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Panel members: Dominique Turck, Torsten Bohn, Jacqueline Castenmiller, Stefaan De Henauw, Karen Ildico Hirsch-Ernst, Helle Katrine Knutsen, Alexandre Maciuk, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Carmen Pelaez, Kristina Pentieva, Alfonso Siani, Frank Thies, Sophia Tsabouri and Marco Vinceti.

Declarations of interest: The declarations of interest of all scientific experts active in EFSA's work are available at https://ess.efsa.europa.eu/doi/doiweb/doisearch.

Acknowledgements: EFSA wishes to acknowledge the contribution of WG on Claims: Jean-Louis Bresson, Stefaan de Henauw, Alfonso Siani and Frank Thies to this opinion.

Suggested citation: EFSA NDA Panel (EFSA Panel on Nutrition, Novel Foods and Food allergen), 2021. Scientific Opinion on MegaNatural®-BP grape seed extract and maintenance of normal blood pressure: evaluation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2021;19(8):6776, 11 pp. https://doi.org/10.2903/j.efsa.2021.6776

ISSN: 1831-4732

The EFSA Journal is a publication of the European Food Safety Authority, a European agency funded by the European Union.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1924/2006 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 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).

1.2. Interpretation of the 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: MegaNatural®-BP and maintenance of normal blood pressure.

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of MegaNatural® grape seed extract, a positive assessment of its safety, nor a decision on whether MegaNatural® grape seed extract 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 18(4) of Regulation (EC) No 1924/2006.

2. Data and methodologies

2.1. Data

Information provided by the applicant

Food/constituent as stated by the applicant

According to the applicant, the food for which the health claim is made is *'MegaNatural®-BP grape seed extract made entirely of California-grown grapes containing biologically active constituents: total phenolics (90–93%), gallic acid (≥ 2%) and catechin and epicatechin (≥ 5%). The distribution of phenolic compounds in the MegaNatural®-BP is on average 9% monomers, 69% oligomers and 22% polymers'*.

Health relationship as claimed by the applicant

According to the applicant, the health effect is related to *'maintenance of normal blood pressure through endothelium dependent vasodilatation. The outcome variables used to establish the claimed effect include multiple ambulatory measurements of systolic and diastolic blood pressure and elevation of oxidized LDL in serum'*.

Mechanism by which the food/constituent could exert the claimed effect as proposed by the applicant

The applicant claims that *'MegaNatural®-BP [is able] to elicit endothelium-dependent relaxation of the blood vessels through its potent antioxidant activity and ability to inhibit endothelin-1 (ET-1) synthesis'*.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: *'MegaNatural®-BP helps maintain healthy blood pressure'*.

Specific conditions of use as proposed by the applicant

According to the applicant, the target population for the intended health claim is healthy adults. The quantity of 300 mg/day is recommended.

Data provided by the applicant

The health claim application on MegaNatural®-BP and maintenance of normal blood pressure pursuant to Article 13.5 of Regulation 1924/2006, was presented in a common and structured format as outlined in the Scientific and technical guidance for the preparation and presentation of applications for authorisation of health claims (EFSA NDA Panel, 2016).

As outlined in the General guidance for stakeholders on health claim applications, it is the responsibility of the applicant to provide the totality of the available evidence.

2.2. Methodologies

The general approach of the NDA Panel for the evaluation of health claim applications is outlined in the EFSA general guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016).

The scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health are outlined in a specific EFSA guidance (EFSA NDA Panel, 2018).

The application does not contain data claimed as proprietary and data claimed as confidential.

3. Assessment

The approach used by the NDA Panel for the evaluation of health claims is explained in the General scientific guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016). In assessing each specific food/health relationship, which forms the basis of a health claim the NDA Panel considers the following key criteria:

i) the food/constituent is defined and characterised;
ii) the claimed effect is based on the essentiality of a nutrient; OR the claimed effect is defined and is a beneficial physiological effect for the target population and can be measured *in vivo* in humans;
iii) a cause and effect relationship is established between the consumption of the food/constituent and the claimed effect (for the target group under the proposed conditions of use).

Each of these three criteria needs to be assessed by the NDA Panel with a favourable outcome for a claim to be substantiated. In addition, an unfavourable outcome of the assessment of criterion (i) and/or (ii) precludes the scientific assessment of criterion (iii).

3.1. Characterisation of the food/constituent

The food/constituent proposed by the applicant as the subject of the health claim is 'MegaNatural®-BP grape seed extract'.

MegaNatural®-BP is made from a blend of freshly crushed, unfermented varietal grapes (lat. *Vitis vinifera*) grown in the Mission Bell Winery in Madera, California, USA. A multi-stage hot-water-based extraction process in different pH environment is used, followed by adsorption by an adsorbent resin (styrene divinyl benzene or trimethylolpropane trimethacrylate). This manufacturing process results in a grape seed extract rich in procyanidolic and catechin monomers and oligomers with minimal content of high molecular polymeric procyanidins (US Patent, 2003).

The final product is standardised for total phenolics (90–93%), gallic acid (≥ 2%) and the sum of catechins and epicatechins (≥ 5%). The distribution of phenolic compounds in MegaNatural®-BP, as measured by high-performance liquid chromatography (HPLC), is on average 9% monomers, 69% oligomers and 22% polymers. The content of the standardised substances is identified by spectrophotometry and/or HPLC-UV.

MegaNatural®-BP is sold as a powder and intended for use as an ingredient in beverages, foods and dietary products. Information related to stability and batch to batch variability was provided.

The Panel considers that the food constituent MegaNatural®-BP, a grape seed extract standardised for total phenolics, gallic acid and the sum of catechin and epicatechin content, which is the subject of the health claim, is sufficiently characterised.

3.2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is 'maintenance of normal blood pressure'. The proposed target population is healthy adults.

'The scientific evidence for the substantiation of health claims on the maintenance of normal BP can be obtained from human intervention studies showing a reduction in SBP (e.g. point SBP, 24-h SBP) or a reduction in diastolic blood pressure (DBP) (e.g. point DBP, 24-h DBP) if accompanied by a reduction in SBP, as compared to an appropriate food/constituent or exceptionally to no intervention (e.g. control group on usual diet). In this context, also reductions in BP within the normal range are considered beneficial physiological effects.

Regarding the study duration, BP tends to stabilise after about 4 weeks in response to fixed nutritional interventions. However, the time needed to reach such stabilisation may depend on the study characteristics (e.g. appropriate run-in period) and the nature of the intervention. Evidence on the sustainability of the effect with continuous consumption of the food/constituent over longer periods of time (e.g. 8 weeks) should be provided.

Studies should be designed to account for intraindividual variability, and BP should be measured using well-accepted methods according to standardised conditions and protocols (Mancia et al.*, 2013). Owing to the lack of standardisation, self (home) measurement of BP (e.g. using an electronic device) is not an appropriate method for measuring point SBP and point DBP in research settings; validation of the device and protocols used are required. Measurement with a calibrated sphygmomanometer (Mancia* et al.*, 2013; Tolonen* et al.*, 2015) is the standard method for the assessment of office BP.*

Ambulatory blood pressure monitoring (ABPM) allows measuring BP over a 24-h period and provides an insight to BP changes during everyday activities not covered by single measurements. The ABPM is an appropriate method for measuring mean 24-h SBP and 24-h DBP.

With respect to the study population, results from studies conducted in hypertensive subjects treated with lifestyle measures only (e.g. diet) could be used for the scientific substantiation of these claims. However, the rationale for extrapolation of results obtained in hypertensive subjects under treatment with blood pressure lowering medications (e.g. angiotensin converting enzyme (ACE) inhibitors, blockers of beta adrenergic receptors, calcium channel blockers and diuretics) to the target population for the claim should be provided and will be considered on a case-by-case basis (e.g. evidence for a lack of interaction between the food and the medications used on the claimed effect' (EFSA NDA Panel, 2018).

The Panel considers that maintenance of normal blood pressure is a beneficial physiological effect.

3.3. Scientific substantiation of the claimed effect

The applicant performed a literature search on 30 August 2020 in the following databases: PubMed, ScienceDirect, Google Scholar and Embase. Keywords used for the food were: 'grape seed extract', 'grape seed polyphenols', 'grape juice', 'MegaNatural®-BP', 'MegaNatural-Gold', and for the endpoint: 'antioxidant', 'atherosclerosis', 'blood pressure', 'hypertension', 'pre-hypertension', 'metabolic syndrome' and 'cardiovascular diseases'. Only articles published in English language were considered. In addition, a manual search was carried out. To retrieve pertinent published human trials the web site www.polyphenolics.com was also searched.

The applicant submitted four human intervention studies and two meta-analyses of human intervention studies. For the purpose of this opinion, only outcomes related to blood pressure are discussed.

The systematic review by Zhang et al. (2016) covered 12 papers including 16 trials and the meta-analysis published by Li et al. (2015) included 10 intervention studies in humans. The Panel notes that most studies included in these meta-analyses were conducted with grape seed extracts and products containing grape polyphenols other than MegaNatural®-BP. The Panel considers that no conclusions can be drawn from these meta-analyses for the scientific substantiation of the claim.

In a randomised, double-blind, parallel, placebo-controlled, 3-arm dose-response study, Sivaprakasapillai et al. (2009) investigated the effect of MegaNatural®-BP on BP in a group of 27 individuals with the metabolic syndrome (9 per arm, 16 women, mean age 46 ± 3 years).

Adult subjects aged 25–80 years meeting the criteria of the National Cholesterol Education Program III (NCEP-III) for the metabolic syndrome were included. Smoking, cardiovascular, pulmonary, gastrointestinal and renal diseases, and chronic use of medicines were exclusion criteria. The publication does not provide information on the recruitment procedure, the process of randomisation, the allocation

of subjects to the study groups, the substance used as placebo, the power calculation, compliance of subjects, or drop-outs during the study.

The participants were randomised to consume MegaNatural®-BP 300 mg/day, MegaNatural®-BP 150 mg/day or placebo (not specified). The intervention lasted 4 weeks. Mean daytime SBP and DBP, measured by daytime 12-h ABPM at baseline and at the end of the intervention, were the primary outcomes of the study. Only within-group statistical analysis using two-way ANOVA is reported for BP. The Panel notes that no between-group comparisons are provided. The Panel also notes that BP at baseline was markedly higher in the MegaNatural®-BP 150 mg group (SBP = 134 ± 5 mmHg, DBP = 83 ± 3 mmHg) than in the MegaNatural®-BP 300 mg (SBP = 123 ± 4 mmHg, DBP = 74 ± 4 mmHg) and the placebo (SBP = 127 ± 4 mmHg, DBP = 78 ± 3 mmHg) groups, which suggests a randomisation failure of the study. Upon a request from EFSA to provide correct statistical analysis, the applicant replied that it was not possible to contact the authors of the study.

The Panel considers that no conclusions can be drawn from this study with severe limitations, including insufficient reporting and inappropriate statistical analysis, for the scientific evaluation of the claim.

The study by Robinson et al. (2012) was a randomised, double-blind, parallel, placebo-controlled, two arm study in 32 participants (n = 16 in each group, mean age 52 ± 3 years, 17 women, no drop-outs) assessing the effect of MegaNatural®-BP on blood pressure in adults with normal and high normal blood pressure.

Adults aged 25–80 years with normal and high normal blood pressure (prehypertension) (SBP between 120 and 139 mmHg and DBP between 80 and 89 mmHg based on 24-h ambulatory blood pressure monitoring (24-h ABPM)) were enrolled. Non-inclusion criteria were smoking, diagnosed cardiovascular, gastrointestinal and renal diseases, and chronic use of medicines. Information on the recruitment procedure, the randomisation process, and the power calculation is lacking in the publication. Upon EFSA's request, the applicant was unable to provide this information.

After a 2-week run-in period, the participants were randomised for an 8-week intervention into two groups receiving one capsule/day of either MegaNatural®-BP (300 mg) or placebo (maltodextrin). Mean daytime SBP and DBP, measured by daytime 12-h ABPM at baseline and at the end of the intervention, were the primary outcomes of the study.

Only within-group statistical analysis using the paired Student's t-test is reported for BP. The Panel notes that no between-group comparisons are provided. Upon a request from EFSA to provide correct statistical analysis, the applicant replied that it was not possible to contact the authors of the study.

The Panel considers that no conclusions for the scientific evaluation of the claim can be drawn from this study with severe limitations, including insufficient reporting and inappropriate statistical analysis.

In a randomised double-blind, parallel, placebo-controlled, two arm study, Ras et al. (2013) assessed the effect of MegaNatural®-BP on blood pressure in adult subjects with normal blood pressure with SBP from 120 to 129 mm Hg and DBP from 80 to 84 mm Hg, high normal blood pressure (SBP ranging from 130 to 139 mm Hg or DBP ranging from 85 to 89 mm Hg) and untreated persons with stage 1 hypertension (SBP 140-159 mmHg and DBP 90–99 mmHg).

Adults aged 35–75 years with no reported current or previous metabolic diseases, mean 6-h ambulatory SBP ranging between 120 and 159 mmHg and DBP < 100 mmHg, and no pharmacological treatment for hypertension, were recruited. Non-inclusion criteria were diagnosed metabolic, cardiovascular, gastrointestinal and renal diseases.

After a run-in period, the participants were randomised on 1:1 basis to consume MegaNatural®-BP (1 capsule – 300 mg/day) or placebo (microcrystalline cellulose – 1 capsule/day) for 8 weeks. A stratification according to sex was used.

Sample size was calculated on 12-h daytime mean SBP measured by ABPM, the primary outcome of the study. Assuming a within-subject variation of 30 mmHg for duplicate ABPM measurements, 70 subjects were needed to detect a mean SBP reduction of 3.7 mmHg (α = 0.05; two-sided) with a statistical power of 80%. Secondary outcomes were plasma renin activity, platelet aggregation and concentrations of alkyldimethylamine (ADMA), nitric oxide metabolites, and urinary phenolic acids.

Blood pressure was measured on two consecutive days at the run-in period and at the end of the intervention (four times) by 12-h daytime ABPM at intervals of 20 min. Mean daytime SBP and DBP were calculated for each individual as the average of all values recorded.

Data were analysed by repeated-measurements mixed-model analysis. Treatment, sex, date of inclusion in the trial and hour of BP measurement were included as fixed factors. Age, BMI, change in body weight, change in urinary Na and K excretion and urinary Na:K ratio were included as covariates.

Participants were included as a random factor. The model was simplified by backward elimination: variables were only retained when their significance was below 0.10.

A total of 70 participants were randomised (n = 35 in each group, 38 males, mean age 63.7 ± 0.8 years). One subject dropped out during the run-in period and was replaced by a spare subject. One participant (in the MegaNatural®-BP group) dropped out during the intervention. The compliance, measured as the number of the capsules returned at the end of the study, was high (99.7%).

The results were provided for the 69 participants who completed the study. Mean daytime SBP decreased from 135.8 ± 1.9 mmHg (mean ± SEM) to 130.3 ± 1.7 mmHg in the MegaNatural®-BP group, and from 135.7 ± 1.7 mmHg to 132.5 ± 1.7 mmHg in the control group during the study. In an adjusted model, with change in mean daytime SBP adjusted for baseline values and the covariates listed above, the change in SBP was –5.2 mmHg (95% CI; –7.7, –2.8) in the MegaNatural®-BP group and –2.2 mmHg (95% CI; –4.7, –0.2) in the placebo group. The difference in SBP changes between groups was –3.0 mmHg (95% CI: –6.5, 0.5; p = 0.09).

Mean daytime DBP decreased from 81.9 ± 1.5 mmHg (mean ± SEM) to 79.1 ± 1.3 mmHg in the MegaNatural®-BP group and from 81.1 ± 1.2 mmHg to 80.0 ± 1.1 mmHg in the control group. In the adjusted model, the change in DBP was –2.5 mmHg (95% CI; –4.0, –1.0) in the MegaNatural®-BP group and –1.1 mmHg (95% CI; –2.4, 0.4) in the placebo group. The difference in DBP changes between groups was –1.4 mmHg (95% CI; –3.5, 0.6; p = 0.18).

The Panel considers that this study does not show an effect of MegaNatural®-BP given at doses of 300 mg/day for 8 weeks on blood pressure in people with normal and high normal blood pressure or stage 1 hypertension.

Park et al. (2016) studied the effect of MegaNatural®-BP on blood pressure in subjects with normal and high normal blood pressure (prehypertension) in a randomised, double-blind, parallel, placebo-controlled, two arm study.

Adults aged 25–65 years with SBP between 120 and 139 mmHg or DBP between 80 and 89 mmHg were enrolled. Non-inclusion criteria comprised smoking, diagnosed cardiovascular, respiratory, gastrointestinal and renal diseases, and chronic use of medicines. Information on the recruitment procedure and the process of allocation of subjects to the study groups is not provided in the publication.

After a 2-week run-in period, the eligible participants were randomised on a 1:1 basis to consume either MegaNatural®-BP (300 mg/day dissolved in 355 mL of fruit juice) or placebo (same amount of fruit juice) for 6 weeks. Subjects were followed for 4-week with no treatment thereafter.

Blood pressure was measured by 24-h ABPM at intervals of 1 h. The measurements were carried out four times (at the screening visit, at the beginning of the intervention, and after 6 and 10 weeks).

Sample size was calculated based on the expected change difference in SBP between groups (the exact values were not presented), with an 80% power, alpha = 0.05, and 20% attrition rate. A total of 34 subjects were estimated to be needed.

Changes in mean daytime and night-time SBP were the primary outcomes. Changes in DBP, flow-mediated dilatation of the brachial artery, presence of slCAM-1 and concentrations of plasma lipids, glucose, insulin, oxLDL, and phenolic compounds and metabolites were treated as secondary outcomes.

In statistical analysis, mixed model analysis of repeated measures was performed on each outcome variable to test the effects of treatment (MegaNatural®-BP, control) and time (weeks). The Kenward–Roger correction and the method of restricted maximum likelihood were used in all mixed models.

In total, 36 adults were randomised (18 subjects per group) and 29 completed the 6-week intervention (12 in the MegaNatural®-BP group and 17 in the control group, mean age 43 ± 10 years, 15 men). The results on BP were reported for completers with successful BP measurements (n = 29 and n = 21 for daytime and night-time BP, respectively). The number of returned bottles was between 80% and 100% in both groups.

The results described below refer to the 6-week intervention period.

Daytime SBP decreased from 125.0 ± 2.3 mmHg (mean ± SEM) to 118.0 ± 2.3 mmHg in the MegaNatural®-BP group and increased from 125.6 ± 1.9 mmHg to 127.0 ± 1.9 mmHg in the control group. The change in daytime SBP was -7.0 ± 3.2 mmHg in the MegaNatural®-BP group and 1.4 ± 2.1 mmHg in the control group (p = 0.003 in the mixed model). SBP values returned to baseline at the end of the 4-week follow-up (124.1 ± 2.0 mmHg).

Night-time SBP decreased from 112.9 ± 2.3 mmHg (mean ± SEM) to 111.5 ± 2.5 mmHg in the MegaNatural®-BP group and decreased from 113.1 ± 2.0 mmHg to 111.2 ± 2.0 mmHg in the control group. The change in night-time SBP was –1.4 ± 2.8 mmHg in the MegaNatural®-BP group and –0.9 ± 2.2 mmHg in the control group (difference not statistically significant in the mixed model).

Daytime DBP decreased from 83.0 ± 1.6 mmHg (mean ± SEM) to 79.1 ± 1.6 mmHg in the MegaNatural®-BP group and increased from 82.9 ± 1.3 mmHg to 83.6 ± 1.3 mmHg in the control group. The change in daytime SBP was –3.9 ± 1.5 mmHg in the MegaNatural®-BP group and 0.7 ± 1.8 mmHg in the control group (difference not statistically significant in the mixed model).

Night-time DBP decreased from 73.1 ± 1.7 mmHg (mean ± SEM) to 72.6 ± 1.9 mmHg in the MegaNatural®-BP group and increased from 73.1 ± 1.5 mmHg to 74.7 ± 1.7 mmHg in the control group. The change in night-time SBP was –0.5 ± 1.8 mmHg in the MegaNatural®-BP group and 1.6 ± 1.5 mmHg in the control group (difference not statistically significant in the mixed model).

The Panel considers that this study performed in adults with normal and high normal blood pressure showed an effect of MegaNatural®-BP given at doses of 300 mg/day for 6 weeks on daytime (and not on night-time) SBP. The Panel notes that no effect was observed on DBP.

The Panel considers that, among the two human intervention studies submitted from which scientific conclusion could be drawn for the scientific substantiation of the claim, one showed an effect of MegaNatural®-BP (300 mg/day) on BP in adults with normal and high normal BP when consumed daily for 6 weeks, whereas the second study did not show an effect of MegaNatural®-BP at the same daily dose consumed for 8 weeks in adults with normal and high normal blood pressure or stage 1 hypertension.

Mechanism of action proposed

The applicant claims that MegaNatural®-BP elicits endothelium-dependent relaxation of the blood vessels through its antioxidant activity and ability to inhibit endothelin-1 (ET-1) synthesis.

In vivo studies in humans

In the study described above, Park et al. (2016) measured the effect of MegaNatural®-BP at 300 mg/day given for 6 weeks on flow-mediated dilation (FMD) in subjects with high normal BP. Despite the reported effect of MegaNatural®-BP on daytime SBP, no effect of MegaNatural®-BP was found on endothelium-dependent FMD compared to placebo. The Panel notes that this study provides no evidence for a mechanism by which MegaNatural®-BP could exert an effect on BP.

Vinson et al. (2001) investigated the effect of MegaNatural® Gold on the total antioxidant capacity of plasma and lipoprotein oxidation as compared to red wine, grape juice and tocopherols. The Panel notes that MegaNatural® Gold is not the food that is the subject of the claim and considers that it is unclear how a change in the variables assessed could affect BP in humans.

In vitro studies

Edirisinghe et al. (2008) added MegaNatural®-BP to rabbit aortic rings suspended in organ baths and pre-contacted with noradrenaline. The extract triggered a dose-dependent relaxation (0.1, 1.0, 10.0 and 100 μmol/L). The magnitude of the effect was similar to the effect exerted by acetylcholine given in the same concentrations. After the removal of endothelium, the relaxation effect disappeared. Also, prior incubation with l-NAME (NG-nitro-L-arginine methyl ester), which is a competitive endothelial nitric oxide synthase inhibitor, suppressed the relaxation effect.

Lindbury and Corder (2002), unpublished study report) found that under *in vitro* conditions, MegaNatural® showed an ability to inhibit ET-1 synthesis in a model of bovine aortic endothelial cells. MegaNatural® incubated with the endothelial cells for 6 h caused a concentration-dependent inhibition of ET-1 synthesis in the concentration range 40–1.25 μg/mL.

The Panel considers that there are significant limitations to these studies. For example, there is no information on how the concentration used in these *in vitro* studies relates to the concentration of MegaNatural®-BP in human serum, the profile of the active component(s) is undefined, and it is not clear whether there are changes from metabolism by, e.g. the liver.

The Panel considers that the results of these *in vitro* studies do not provide sufficient evidence for a mechanism by which MegaNatural®-BP could exert an effect on BP *in vivo* in humans.

The Panel considers that overall, the evidence provided did not establish a plausible mechanism by which the food could exert the claimed effect *in vivo* in humans.

Weighing the evidence

In weighing the evidence, the Panel took into account that among the two human intervention studies submitted from which scientific conclusion could be drawn for the scientific substantiation of the claim, one showed an effect of MegaNatural®-BP (300 mg/day) on BP in adults with normal and high normal BP when consumed daily for 6 weeks, whereas the second study did not show an effect

of MegaNatural®-BP at the same daily dose consumed for 8 weeks in adults with normal, high normal blood pressure or stage 1 hypertension. The Panel also took into account that the evidence provided did not establish a plausible mechanism by which the food could exert the claimed effect *in vivo* in humans.

The Panel concludes that the evidence provided is insufficient to establish a cause and effect relationship between the consumption of MegaNatural®-BP, a grape seed extract standardised for total phenolics, gallic acid and the sum of catechin and epicatechin content, and maintenance of normal blood pressure.

Conclusions

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

- The food/constituent, MegaNatural®-BP, grape seed extract standardised for total phenolics, gallic acid and the sum of catechin and epicatechin content, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect proposed by the applicant is 'maintenance of normal blood pressure'. The target population proposed by the applicant is the adult population. Maintenance of normal blood pressure is a beneficial physiological effect.
- The evidence provided is insufficient to establish a cause and effect relationship between the consumption of MegaNatural®-BP, a grape seed extract standardised for total phenolics, gallic acid and the sum of catechin and epicatechin content, and maintenance of normal blood pressure.

Documentation as provided to EFSA

Health claim application on pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0501_HR). Submitted by Praline i Čokolada j.d.o.o., Glavna ulica 64c, 10360 Sesvete, Croatia.

Steps taken by EFSA

1) This application was received by EFSA on 30/10/2020.
2) The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.
3) The scientific evaluation procedure started on 2/03/2021.
4) On 15/04/2021, 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 scientific evaluation was suspended on 5/05/2021 and was restarted on 16/05/2021, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
5) During its meeting on 6/07/2021, the NDA Panel, having evaluated the data, adopted an opinion on the scientific substantiation of a health claim related to the consumption of MegaNatural®-BP, grape seed extract standardised for total phenolics, gallic acid and the sum of catechin and epicatechin content, and maintenance of normal blood pressure.

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Abbreviations

ABPM	ambulatory blood pressure monitoring
ACE	angiotensin-converting enzyme
ADMA	alkyldimethylamine
ANOVA	analysis of variance
BMI	Body Mass Index
BP	blood pressure
CI	confidence interval
DBP	diastolic blood pressure
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ET-1	endothelin-1
FMD	flow-mediated dilation
HPLC	high-performance liquid chromatography
ICAM-1	inter cellular adhesion molecule
l-NAME	NG-nitro-L-arginine methyl ester
LDL	low-density lipoprotein
NCEP-III	National Cholesterol Education Program III
NDA	Panel on Nutrition, Novel Foods and Food Allergens
SBP	systolic blood pressure
SEM	standard error to the mean
UV	ultraviolet