Black tea and maintenance of normal endothelium-dependent vasodilation: evaluation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006

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Abstract

Following an application from Unilever NV, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Ireland, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to black tea and maintenance of normal endothelium-dependent vasodilation. The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The food proposed by the applicant as the subject of the health claim is black tea beverages, either freshly prepared or reconstituted from water extract powders of black tea, characterised by the content of flavanols (expressed as catechins plus theaflavins) of at least 30 mg per 200 mL serving. The Panel considers that black tea characterised by the content of flavanols (expressed as catechins plus theaflavins) is sufficiently characterised. The claimed effect proposed by the applicant is ‘improvement of endothelium-dependent vasodilation’. The Panel considers that maintenance of normal endothelium-dependent vasodilation is a beneficial physiological effect. Of the five human intervention studies provided on the chronic effect of black tea consumption on endothelium-dependent vasodilation, two investigated the effect after regular consumption of black tea for a sufficiently long time period (i.e. at least 4 weeks). These two studies did not allow an effect of black tea on endothelium-dependent vasodilation to be established. The Panel concludes that a cause and effect relationship has not been established between the consumption of black tea and maintenance of normal endothelium-dependent vasodilation.

Keywords: tea, flavanols, tea, endothelium, vasodilation, health claim

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Summary

Following an application from Unilever NV, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Ireland, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to black tea and maintenance of normal endothelium-dependent vasodilation.

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

The general approach of the NDA Panel for the evaluation of health claims applications is outlined in the EFSA general guidance for stakeholders on health claim applications and the guidance on the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health.

The food proposed by the applicant as the subject of the health claim is black tea beverages, either freshly prepared or reconstituted from water extract powders of black tea, characterised by the content of flavanols (expressed as catechins plus theaflavins) of at least 30 mg per 200 mL serving. The Panel considers that black tea characterised by the content of flavanols (expressed as catechins plus theaflavins) of ≥ 30 mg/200 mL serving, which is the subject of the health claim, is sufficiently characterised.

The claimed effect proposed by the applicant is ‘improvement of endothelium-dependent vasodilation’. The proposed target population is ‘adults in the general population’. The Panel considers that maintenance of normal endothelium-dependent vasodilation is a beneficial physiological effect.

The applicant identified as directly pertinent to the claim five human intervention studies on the effect of black tea consumption on endothelium-dependent vasodilation measured in fasting conditions after regular consumption of black tea (chronic effect) and four human intervention studies on the acute effect of black tea consumption on endothelium-dependent vasodilation after regular consumption of black tea (acute-in-chronic effect). In addition, the applicant provided eight human intervention studies on the acute effects of tea beverages on endothelium-dependent vasodilation as supportive evidence. The applicant also submitted meta-analyses of the chronic, acute-in-chronic studies and acute studies, both individually and combined.

Out of the five human intervention studies provided on the chronic effect of black tea consumption on endothelium-dependent vasodilation, only two investigated the effect after regular consumption of black tea for a sufficiently long time period (i.e. at least four weeks).

In one of these studies, an effect of black tea consumption not only on endothelium-dependent vasodilation but also on endothelium-independent vasodilation was observed. Therefore, this study did not allow conclusions to be drawn on whether the effects of black tea consumption on vasodilation were endothelium dependent or mediated via endothelium-independent pathways. The Panel considers that no conclusions can be drawn from this study on the effect of black tea consumption on endothelium-dependent vasodilation. The second study in which black tea was consumed for 6 months did not show an effect of black tea consumption on endothelium-dependent vasodilation.

In the absence of studies allowing an effect of black tea consumption to be established on endothelium-dependent vasodilation in fasting conditions in healthy individuals after regular consumption of the food for at least 4 weeks, the Panel considered that studies of shorter duration, on an acute effect of black tea consumption with or without preceding continued consumption of the food, or in patients, as well as the meta-analysis provided by the applicant cannot be used for the scientific substantiation of the claim.

In weighing the evidence, the Panel took into account that the two studies which were provided by the applicant and which investigated the effect of black tea consumption on endothelium-dependent flow-mediated dilation in fasting conditions after regular consumption of the food for at least four weeks did not allow an effect of black tea on endothelium-dependent vasodilation to be established.

On the basis of the data provided, the Panel concludes that a cause and effect relationship has not been established between the consumption of black tea and maintenance of normal endothelium-dependent vasodilation.
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1. Introduction

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

Regulation (EC) No 1924/2006\(^1\) 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).

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: black tea and improvement of endothelium-related vasodilation.

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of black tea, a positive assessment of their safety, nor a decision on whether black tea 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 ‘catechins and theaflavins found in beverages prepared from the leaves of Camellia sinensis (L.) Kuntze’. Following EFSA’s request for clarification, the applicant indicated that the food for which the health claim is made is ‘black tea beverages characterised by the content of flavanols (expressed as catechins plus theaflavins)’.

Health relationship as claimed by the applicant

According to the applicant, the claimed effect relates to: ‘improvement of endothelium-dependent vasodilation’.

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

The applicant claims that ‘the available evidence demonstrates that flow-mediated dilation is increased acutely after consumption of tea flavanols and this effect is still present after regular consumption for longer periods of time’.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: ‘improves endothelium-dependent vasodilation which contributes to healthy blood flow’.

**Specific conditions of use as proposed by the applicant**

According to the applicant, the target population for the intended health claim is adults in the general population and a daily intake of ~160 mg tea flavanols (approx. 1,090 mL (5–6 servings) of black tea) is required to obtain a physiologically relevant increase of 1% in flow-mediated dilation (FMD).

**Data provided by the applicant**

Health claim application on tea flavanols and improvement of endothelium-related vasodilatation pursuant to Article 13.5 of Regulation 1924/2006, 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, 2011a).

As outlined in the General guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016), it is the responsibility of the applicant to provide the totality of the available evidence.

### 2.2. Methodologies

The general approach of the Dietetic Products, Nutrition and Allergies (NDA) Panel for the evaluation of health claims 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, 2011b).

The application contains data claimed as confidential:

- a) Unpublished consumer research.
- b) Analytical technique for the determination of the flavin content of black and green teas.
- c) Unpublished compositional data of a range of black and green teas.

### 3. Assessment

#### 3.1. Characterisation of the food/constituent

The food proposed by the applicant as the subject of the health claim is ‘catechins and theaflavins found in beverages prepared from the leaves of *Camellia sinensis* (L.) Kuntze’.

The main catechins in tea include (-)-epigallocatechin gallate, (-)-epigallocatechin, (-)-epicatechin-3-O-gallate, (-)-epicatechin, (+)-gallocatechin and (+)-catechin. The major theaflavins are theaflavin, theaflavin-3-O-gallate, theaflavin-3′-O-gallate and theaflavin-3,3′-O-digallate. Black tea also contains thearubigins, believed to constitute about 60% of black tea solids (Haslam, 2003).

Upon a request from EFSA to clarify whether the claim refers to tea flavanols (including catechins, theaflavins and thearubigins), to a fixed combination of catechins and theaflavins in tea or to tea beverages made from the leaves of *Camellia sinensis* (L.) Kuntze characterised by their content in catechins and theaflavins, the applicant replied that the food that is the subject of the claim is black tea beverages, either freshly prepared or reconstituted from water extract powders of black tea, characterised by the content of flavanols (expressed as catechins plus theaflavins) of at least 30 mg per 200 mL serving.

Catechins and theaflavins can be measured in foods by well-established methods. The Panel notes that catechins are absorbed after oral consumption, whereas the absorption of theaflavins in the small intestine is low (Mulder et al., 2001). Theaflavins persist to the colon, where they undergo catabolism by gut microbiota (van Duynhoven et al., 2011; Chen et al., 2012; Del Rio et al., 2013). There is some evidence that the gut microbial catabolites of black tea polyphenols are recirculated into plasma (van Duynhoven et al., 2014).

The Panel considers that black tea characterised by the content of flavanols (expressed as catechins plus theaflavins) of ≥ 30 mg/200 mL 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 ‘improvement of endothelium-related vasodilation’. The proposed target population is ‘adults in the general population’.
Improvement of endothelium-dependent (ED) vasodilation, which is a specific endothelial function, can be measured in vivo in humans using well-accepted methods. The capacity of blood vessels to respond to physical and chemical stimuli in the lumen confers the ability to self-regulate tone and to adjust blood flow and distribution in response to changes in the local environment. Many blood vessels respond to an increase in flow, or more precisely shear stress, by dilating. This phenomenon is designated as FMD. A principal mediator of FMD is endothelium-derived nitric oxide (NO). Endothelial denudation or treatment with a nitric oxide synthase (NOS) inhibitor abolishes FMD in a variety of arterial vessels. Endothelium-derived prostanoids and the putative endothelium-derived hyperpolarising factor have also been implicated as backup mechanisms mediating changes in arterial diameter in response to shear stress, so that there may be some redundancy in the system in order to ensure an appropriate response of blood vessels to shear stress. ED vasodilation contributes to the maintenance of an adequate blood flow to body cells and tissues.

ED vasodilation can be assessed in vivo at different points of the arterial tree using well-established methods (e.g. the FMD technique). Endothelium-independent vasodilation (EIVD) of the brachial artery induced by exogenous NO donors (e.g. after the sublingual administration of nitroglycerin) is also measured as control (Corretti et al., 2002; Thijssen et al., 2011).

The effect of a food/constituent on ED vasodilation can be expressed as changes in ED-FMD either in fasting conditions after regular consumption of the food/constituent, or as acute changes in ED-FMD occurring shortly after consumption of the food/constituent. A sustained increase in ED vasodilation in fasting conditions in response to an intervention (regular consumption of a food/constituent for at least four weeks) is a beneficial physiological effect.

Markers of plasma NO status (e.g. nitrite/nitrosyl species measured by reductive gas-phase chemiluminescence) can provide evidence on the mechanisms by which the food/constituent could exert the claimed effect, but cannot be used alone for the substantiation of the claim.

The Panel considers that maintenance of normal ED vasodilation is a beneficial physiological effect.

### 3.3. Scientific substantiation of the claimed effect

The applicant performed a literature search in Medline, Embase, Chemical Abstracts and Biosis (from starting date of the databases until July 2016) with the following key words: (tea or black tea or green tea or flavonoid or tea extract or tea component or tea solid or Camellia sinensis) and (flow-mediated or flow mediated or FMD or endothelial function or endothelial dysfunction or endothelium-dependent or blood flow or arterial stiffness or vascular resistance or circulat* or micro-circulat* or vasodilat* or dilat*). No restrictions were applied. Hand searches were also performed.

In the original application, the applicant had identified 15 published and three unpublished human intervention studies as well as one published and one unpublished meta-analysis as pertinent to the claim. These included studies investigating the effects of green tea, black tea or tea flavonols on ED-FMD. Following EFSA’s request and the applicant’s clarification that the food that is the subject of the claim is black tea beverages, the applicant identified as directly pertinent to the claim five human intervention studies on the effect of black tea consumption on ED-FMD measured in fasting conditions after regular consumption of black tea (chronic effect) (three published (Duffy et al., 2001; Hodgson et al., 2005; Bohn et al., 2014), two unpublished (Mulder et al., 2013, unpublished; Mulder and Dutman, 2014, unpublished)) and four human intervention studies on the acute effect of black tea consumption on ED-FMD after regular consumption of black tea (acute-in-chronic effect) (two published (Grassi et al., 2009, 2016) and two unpublished (Mulder et al., 2013, unpublished; Mulder and Dutman, 2014, unpublished)). In addition, the applicant provided eight human intervention studies on the acute effects of tea beverages on ED-FMD (Duffy et al., 2001; Hodgson et al., 2005; Ardalan et al., 2007; Lorenz et al., 2007; Jochmann et al., 2008; Mulder and Dutman, 2014, unpublished; Mulder et al., 2016, unpublished) as supportive evidence. The applicant also submitted meta-analyses of the chronic, acute-in-chronic studies and acute studies, both individually and combined.

The Panel notes that the study by Ardalan et al. (2007) was not randomised and consisted of a sequential administration of the test products. The Panel considers that no conclusions can be drawn from this study for the substantiation of the claim.

The Panel considers that human intervention studies in healthy individuals on the effect of black tea consumption on ED-FMD measured in fasting conditions after regular consumption of black tea of at least 4 weeks are directly pertinent to the claim, while studies of shorter duration, on the acute effects of black tea on ED-FMD with or without preceding regular consumption of the food or studies in...
patients can provide additional information, but are not sufficient on their own to establish an effect of the food on ED vasodilation.

Among the studies provided by the applicant, two investigated the effect of black tea consumption on ED-FMD measured in fasting conditions after regular consumption of black tea of at least 4 weeks.

Hodgson et al. (2002) studied the effect of consuming black tea for 4 weeks in five servings per day (250 mL per serving; in total 1250 mL, estimation of the flavanol content provided by the applicant complying with the specifications for the food being the subject of the claim; claimed as confidential) in 21 subjects (10 in black tea group and 11 in hot water group, mean age ~59 years, 16 men), who were regular tea drinkers, in a randomised, single-blind (blinded to staff performing measurements), parallel design. The infusion time for black tea was one minute with constant movement. During the study period, subjects were instructed not to consume any caffeinated beverages other than the tea beverage to which they were assigned and not to change their habitual diet.

Measurements of endothelial function of the left brachial artery after an overnight fast were obtained at the end of the baseline period and at the end of the intervention period. EIVD of the brachial artery was measured following administration of 400 μg of sublingual glyceryl trinitrate (GTN) spray. Analysis of ED-FMD and of GTN-mediated dilation was carried out using a semi-automated edge-detection software system. The sample size of the study was sufficient to detect an absolute 1.5% improvement in FMD and an absolute 4.5% improvement in the response to GTN with an 80% power (α = 0.05).

General linear models were used to examine differences in post-intervention values after adjustment for baseline values. The Panel notes that baseline FMD was different between groups (mean ± SE: 5.1% ± 1.0% in the black tea group and 6.1 ± 0.9% in the hot water group).

Consumption of black tea resulted in a significant increase in FMD with an absolute change of 2.3% (95% CI 0.7 to 3.9%). In one subject in the tea group, a large increase in ED-FMD was observed. When this subject was removed from analysis, the increase in ED-FMD still remained significant.

The increase in the response to GTN was also significantly higher in the black tea group compared with the hot water group (mean ± SE: 22.1 ± 2.0% vs. 16.9 ± 0.9%, p = 0.03). Upon a request from EFSA to comment on the biological plausibility of the differential responses to GTN in the study groups, the applicant explained that the finding may potentially be related to the high dose of GTN used in this study (400 μg while 25 μg is the dose generally recommended), which, according to the applicant, elicits very large and therefore inherently noisier brachial artery dilation responses and might lead to spurious conclusions. The Panel notes that even if the dose of GTN used in the study might have led to more variable brachial artery dilation responses among individuals, this would not have been expected to be different between groups and cannot explain the differential response to GTN administration of the black tea and the hot water group.

The Panel notes that this study showed an effect of black tea consumption for 4 weeks on vasodilation. However, owing to the significant differences observed between groups on EIVD, the Panel notes that results of the study do not allow conclusions to be drawn on whether the effects of black tea consumption on vasodilation were ED or mediated via endothelium-independent pathways. The Panel considers that no conclusions can be drawn from this study on the effect of black tea consumption on ED vasodilation.

Bohn et al. (2014) performed a randomised, two-arm, placebo-controlled, double-blind, 6-month parallel trial to investigate the long-term effects of daily consumption of black tea in 111 healthy subjects who were regular tea drinkers. The primary outcome was changes in 24 h systolic blood pressure, upon which also sample size calculations were based. ED-FMD was a secondary outcome.

The participants were randomly allocated to drink three servings of black tea prepared from black tea powder by adding 100–200 mL of hot water (containing 429 mg of polyphenols assessed as gallic acid equivalents and 96 mg of caffeine/day) or a placebo beverage containing no tea solids, but was matched in flavour and caffeine content. During the study period, subjects were asked to restrict the intake of tea, coffee, red wine, chocolate and fruit juices.

ED-FMD was measured at baseline and at 3 and 6 months of the intervention after overnight fasting and was assessed as maximum diameter (max. FMD diameter) and maximum dilation relative to vessel size (Peak FMD). Analysis was carried out using a semi-automated edge-detection software system. EIVD was not measured.

Data were analysed using a linear mixed model. Statistical analysis were performed on the per protocol population (77 participants (38 black tea group and 39 placebo group) mean age ~ 56 years,
50 females) that was defined as all participants who completed the 6-month study, had measurements performed for the relevant outcome and consumed at least 70% of the study product.

No statistically significant changes in ED-FMD were found after having consumed black tea for 3 and for 6 months.

The Panel notes that this study did not show an effect of black tea consumption on ED-FMD.

The Panel notes that none of studies showed an effect of black tea consumption on ED vasodilation in fasting conditions in healthy individuals after regular consumption of the food for at least 4 weeks. In this context, studies of shorter duration (i.e. one week (Mulder et al., 2013, unpublished; Mulder and Dutman, 2014, unpublished; Grassi et al., 2016)), on an acute effect of black tea consumption with or without preceding regular consumption of the food (Lorenz et al., 2007; Jochmann et al., 2008; Grassi et al., 2009; Mulder et al., 2013, unpublished; Mulder and Dutman, 2014, unpublished; Grassi et al., 2016; Mulder et al., 2016, unpublished), or in patients (Duffy et al., 2001; Hodgson et al., 2005), as well as the meta-analyses provided by the applicant cannot be used for the scientific substantiation of the claim.

Weighing of the evidence

In weighing the evidence, the Panel took into account that the two studies from which conclusions can be drawn for the effect of black tea consumption on ED-FMD in fasting conditions after regular consumption of the food for at least 4 weeks did not show effect of black tea on ED vasodilation.

The Panel concludes that a cause and effect relationship has not been established between the consumption of black tea and maintenance of normal ED vasodilation.

4. Conclusions

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

- The food/constituent, black tea characterised by the content of flavanols (expressed as catechins plus theaflavins) of ≥ 30 mg/200 mL which is the subject of the health claim, is sufficiently characterised.
- The claimed effect proposed by the applicant is ‘improvement of endothelium-dependent vasodilation’. The target population proposed by the applicant is ‘adults in general population’. Maintenance of normal ED vasodilation is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of black tea and maintenance of normal ED vasodilation.

Steps taken by EFSA


1) This application was received by EFSA on 16/5/2017.
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 27/6/2017.
4) On 6/9/2017, 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 2/10/2017 and was restarted on 16/10/2017, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
5) During its meeting on 13/12/2017, the NDA Panel, having evaluated the data, adopted an opinion on the scientific substantiation of a health claim related to black tea and improvement of ED vasodilatation.

References


Abbreviations

ED  endothelium dependent
EIVD  endothelium-independent vasodilation
FMD  flow-mediated dilation
GTN  glycercyl trinitrate
NDA  EFSA Panel on Dietetic Products, Nutrition and Allergies
NO  nitric oxide
NOS  nitric oxide synthase