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European Food Safety Authority

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to olive (*Olea europaea* L.) leaf water extract and increase in glucose tolerance pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

*This scientific output, published on 23 July 2014, replaces the earlier version published on 5 May 2014**

ABSTRACT

Following an application from Comvita New Zealand Limited, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of the United Kingdom, 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 olive (*Olea europaea* L.) leaf water extract and increase in glucose tolerance. The food that is the subject of the health claim, olive leaf water extract standardised by its content of oleuropein, is sufficiently characterised. The claimed effect, an increase in glucose tolerance, is a beneficial physiological effect as long as serum insulin concentrations are not disproportionately increased. One human intervention study showed an increase in glucose tolerance without disproportionate increase in insulin concentrations after daily consumption of the olive leaf water extract for 12 weeks under the conditions of use proposed by the applicant. However, the results have not been replicated in other studies, and no evidence has been provided in relation to the mechanism by which the olive leaf water extract could exert the claimed effect. The scientific evidence is insufficient to establish a cause and effect relationship between the consumption of olive leaf water extract and an increase in glucose tolerance.

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KEY WORDS

olive leaf water extract, oleuropein, glucose tolerance, health claim

[1] On request from the Competent Authority of the United Kingdom following an application by Comvita New Zealand Limited, Question No EFSA-Q-2013-00783, adopted on 10 April 2014.

[2] Panel members: Carlo Agostoni, Roberto Berni Canani, Susan Fairweather-Tait, Marina Heinonen, Hannu Korhonen, Sébastien La Vieille, Rosangela Marchelli, Ambroise Martin, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Sean (J.J.) Strain, Inge Tetens, Daniel Tomé, Dominique Turck and Hans Verhagen. Correspondence: nda@efsa.europa.eu

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

* An editorial amendment was carried out that does not materially affect the contents or outcome of this Scientific Opinion. To avoid confusion, the original version has been removed from the EFSA Journal, but is available on request, as is a version showing all the changes made.

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SUMMARY

Following an application from Comvita New Zealand Limited, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of the United Kingdom, 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 olive leaf water extract and increase in glucose tolerance.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application includes a request for the protection of proprietary data.

The food that is the subject of the health claim is olive (*Olea europaea* L.) leaf water extract standardised by its content of oleuropein. The Panel considers that the food, an olive leaf water extract (standardised by its content of oleuropein), which is the subject of the health claim, is sufficiently characterised.

The claimed effect proposed by the applicant refers to "reduces the glycaemic response following carbohydrate consumption". The target population is adults willing to reduce their glycaemic response. Upon request by EFSA for clarification, the applicant indicated that the claimed effect relates to a long-term increase in glucose tolerance, which could be assessed *in vivo* in humans by an oral glucose tolerance test (OGTT) following chronic consumption (e.g. 12 weeks) of the food that is the subject of the health claim. The Panel considers that an increase in glucose tolerance is a beneficial physiological effect as long as serum insulin concentrations are not disproportionately increased.

The applicant identified two human studies and three animal studies as being pertinent to the claim. The Panel considers that no conclusion could be drawn from one human study and from the three animal studies as they were conducted with foods which do not comply with the specifications provided by the applicant in relation to the food that is the subject of the health claim. The Panel considers that the other human study shows an increase in glucose tolerance without disproportionate increase in insulin concentrations after consuming the water extract of fresh olive leaves daily for 12 weeks under the conditions of use proposed by the applicant.

The applicant proposed three mechanisms by which olive leaf water extract could exert the claimed effect: (1) through an acute increase in interleukin 6 (IL-6) in skeletal muscle after exercise, which could improve insulin-regulated glucose metabolism in the muscle; (2) through decreased carbohydrate absorption by inhibiting α-glucosidase in the gut, salivary or intestinal α-amylase activity, or stimulating hepatic glycogen synthesis; and (3) through increasing the activity of hepatic antioxidant enzymes. The Panel considers that the information supplied by the applicant did not provide evidence for the mechanism by which the olive leaf water extract could exert the claimed effect.

On the basis of the data presented, the Panel concludes that the scientific evidence is insufficient to establish a cause and effect relationship between the consumption of olive leaf water extract and an increase in glucose tolerance.

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BACKGROUND

Regulation (EC) No 1924/2006[4] 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 25/09/2013.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.
- The scientific evaluation procedure started on 25/10/2013.
- On 22/01/2014, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application, and the clock was stopped on 29/01/2013, in compliance with Art. 18(3) of Regulation (EC) No 1924/2006.
- On 13/02/2014, EFSA received the requested information as submitted by the applicant and the clock was restarted.
- During its meeting on 10/04/2014, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to olive leaf water extract and increase in glucose tolerance.

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 olive leaf water extract and increase in glucose tolerance.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of olive leaf water extract, a positive assessment of its safety, *nor a decision on whether olive leaf water 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.

[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.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Comvita New Zealand Limited, 23 Wilson Road South, Paengaroa, Bay of Plenty, 3189, New Zealand.

The application includes a request for the protection of proprietary data for bioavailability data and one unpublished study (Lockyer, 2012) in accordance with Article 21 of Regulation (EC) No 1924/2006.

Food as stated by the applicant

According to the applicant, the food is "polyphenol-rich water extract of fresh olive leaf (*Olea europaea* L.)". The extract consists of a complex mixture of polyphenols and is standardised by its content of oleuropein (at least 50 mg per daily intake). The composition of olive leaf extract varies, but in all olive leaf extract products oleuropein is the principal component, normally contributing 20–40 % of the total phenolics present.

Health relationship as claimed by the applicant

According to the applicant, "regular (daily) consumption of polyphenol-rich water extract of fresh olive leaf reduces the glycaemic response following carbohydrate consumption".

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wordings for the health claim: "daily intake of supplemental olive leaf extract polyphenols contributes to the reduction of the blood glucose rise after meals".

Specific conditions of use as proposed by the applicant

The applicant has proposed a daily intake of five Comvita OLE capsules, each containing 400 mg OLE (olive leaf extract) as 6:1 concentrate, equivalent to 2.4 g fresh leaf, with a daily intake providing at least 50 mg oleuropein. The target population is adults willing to reduce their post-prandial glycaemic response. It will be particularly beneficial to individuals with impaired glucose tolerance, a common condition in the general adult population, particularly among those who are overweight or obese.

ASSESSMENT

1. Characterisation of the food

The food that is the subject of the health claim is "polyphenol-rich water extract of fresh olive leaf (*Olea europaea* L.)", OLE. The product is a soft gel capsule containing 400 mg OLE as 6:1 concentrate, equivalent to 2.4 g fresh leaf. The food is standardised by its content of oleuropein.

The Panel notes that the major phenolic constituents in olive leaves are the glycosylated forms of oleuropein (Visioli et al., 2002; Vissers et al., 2002; de Castro and Capote, 2010). Oleuropein is the elenolic acid ester of hydroxytyrosol, representing 1–14 % of olive leaf weight. The composition of commercial olive leaf extracts varies, with oleuropein normally contributing 20–40 % of the total phenolic compounds (Benavente-Garcia, 2000; Lockyer et al., 2012). Depending on the olive tree variety, the harvesting season, the stage of leaf maturity, the storage conditions and the extraction method used, the content of oleuropein may vary greatly in the olive leaf extracts.

Upon request by EFSA, the applicant confirmed that the amount of oleuropein in one capsule of 2.4 g olive leaf water extract is 9.5–16.7 mg (batch-to-batch analysis). In addition, the applicant stated that, owing to a recent change in the leaf harvesting technique, the oleuropein content in the capsules had increased to an average of 24.1 mg/capsule (five batches analysed).

The oleuropein content in the capsules was measured using established methods. The applicant provided information about stability of the product over 24 months. Olive leave polyphenols are absorbed, as polyphenol metabolites were measured in plasma and urine after oral consumption.

The Panel considers that the food, an olive (*Olea europaea* L.) leaf water extract standardised by its content of oleuropein, which is the subject of the health claim is sufficiently characterised

2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant refers to "reduces the glycaemic response following carbohydrate consumption". The target population is adults willing to reduce their glycaemic response.

Upon request by EFSA for clarification, the applicant indicated that the claimed effect relates to a long-term increase in glucose tolerance, which could be assessed in humans by an oral glucose tolerance test (OGTT) following chronic consumption (e.g. 12 weeks) of the food that is the subject of the health claim.

The Panel notes that a long-term increase in glucose tolerance is a beneficial physiological effect as long as serum insulin concentrations are not disproportionately increased. The scientific evidence for the substantiation of health claims related to an increase in glucose tolerance can be obtained from human intervention studies showing a decrease in blood glucose concentrations at different time points during a standard (WHO, 1999) OGTT and with no disproportionate increase in insulin concentrations following chronic consumption (at least 12 weeks) of the food that is the subject of the health claim.

The Panel considers that an increase in glucose tolerance is a beneficial physiological effect as long as serum insulin concentrations are not disproportionately increased.

3. Scientific substantiation of the claimed effect

The applicant performed a literature search in Medline, Embase, Embase Alert and Cochrane Library databases using the following key terms: olive leaf extract, *Olea europaea*, oleuropein, glucose and insulin, with a time period from 1980 to present, published in English. A manual search of review articles was also performed. Exclusion and inclusion criteria applied to select the pertinent publications were reported.

The applicant identified two human studies (Komaki et al., 2003; de Bock et al., 2013), and three animal studies (Komaki et al., 2003; Poudyal et al., 2010; Wainstein et al., 2012) as being pertinent.

In a randomised, double-blind, placebo-controlled, crossover, two-arm human intervention study (de Bock et al., 2013), 46 overweight male volunteers (mean age 46.4 ± 5.5 years, body mass index (BMI) 28.0 ± 2.0) consumed once a day four capsules of olive leaf water extract suspended in safflower oil (containing 51.1 mg oleuropein) or four capsules containing placebo (safflower oil only) for 12 weeks, crossing over to the other intervention after a six-week washout. The exclusion criteria were tobacco use, diabetes or being on medications likely to affect insulin sensitivity. Subjects taking antihypertensive or lipid-lowering medications were recruited, but were required to have been on a stable dose for at least six months prior to the start of the study. At the beginning of the study and at the end of each intervention phase, glucose and insulin concentrations were measured in blood samples taken at baseline and at 30-minute intervals for 2 hours during a standard OGTT with 75 g of glucose; body composition was assessed by dual-energy X-ray absorptiometry (DXA); physical activity levels were scored using the International Physical Activity Questionnaire (IPAQ), which covers four domains of physical activity: work-related, transportation, housework/gardening and leisure time. Three-day dietary records were collected at baseline and at clinical assessment following each 12-week intervention. Fasting blood lipids, insulin-like growth factor I (IGF-I), IGF-II, IGF-binding protein 1 (IGFBP-1), IGFBP-2, IGFBP-3, ultra-sensitive C-reactive protein (CRP), tumour necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), interleukin 8 (IL-8), as well as 24-hour

ambulatory blood pressure and the carotid intima–media thickness, were also measured at the beginning of the study and at the end of each intervention phase.

Sample size was calculated for the primary outcome of the study, the surrogate index of whole-body insulin sensitivity, $ISI_{(composite)}$, which is calculated considering fasting plasma glucose and insulin concentrations, as well as mean plasma glucose and insulin concentrations during the standard OGTT as described by Matsuda and DeFronzo (1999). Considering a mean adult $ISI_{(composite)}$ of 15.6 and a standard deviation (SD) of 8.7, it was calculated that 46 subjects would be needed to detect a 25 % difference between the intervention and placebo with 80 % power at a 0.05 significance level. Secondary outcomes included the areas under the curve (AUC) for glucose and insulin during the OGTT, circulating cytokines, lipid profile, body composition, 24-hour ambulatory blood pressure and carotid intima–media thickness. Linear mixed models were used to assess the main treatment effect accounting for randomisation sequences and time periods, while adjusting for baseline values of the outcome being assessed. On-going use of medication (for cholesterol or hypertension), IPAQ scores, age and per cent body fat were also added as covariates in the analyses.

Three subjects dropped out while taking placebo, one during period 1 (because of injury) and two after crossing over (one was lost to follow-up and one because of development of acne). Statistical analyses were performed in 45 participants. Compliance with the study products was > 96 %. The $ISI_{(composite)}$ was significantly higher after consumption of the olive leaf water extract than after consumption of placebo (+15 %, 5.46 vs. 4.73; $p = 0.024$). The Panel notes that this between-groups difference was lower than the 25 % considered meaningful for power calculations. The AUC for both glucose and insulin were significantly lower following consumption of the olive leaf water extract than following consumption of placebo (–6 % ($p = 0.008$) and –14 % ($p = 0.041$), respectively), which was consistent with significantly lower glucose concentrations at 30 minutes (–6 %; $p = 0.008$) and 60 minutes (–10 %; $p = 0.005$), and with lower insulin concentrations at 60 minutes (–23 %; $p = 0.004$). There were no significant changes in any of the other variables (including per cent body fat and physical activity), except for IL-6, IGFBP-1 and IGFBP-2, which were significantly higher after consumption of the olive leaf water extract than after consumption of placebo.

The Panel considers that this study shows an increase in glucose tolerance without disproportionate increase in insulin concentrations after consuming the water extract of fresh olive leaves daily for 12 weeks under the conditions of use proposed by the applicant.

The other human intervention study (Komaki et al., 2003) in healthy adult subjects and three animal studies (Komaki et al., 2003; Poudyal et al., 2010; Wainstein et al., 2012) assessed the effects of powdered olive leaves or of ethanol or hexane/ethanol extracts of olive leaves on blood glucose concentrations following acute (Komaki et al., 2003) or chronic (14–16 weeks) consumption (Poudyal et al., 2010; Wainstein et al., 2012). The Panel notes that all of these studies were conducted with foods which did not comply with the specifications provided by the applicant in relation to the food that is the subject of the health claim. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim.

With respect to the mechanisms by which the olive leaf water extract could exert the claimed effect, the applicant proposed three mechanisms. First, the applicant proposed that an acute increase in IL-6 in skeletal muscle after exercise could improve insulin-regulated glucose metabolism in the muscle, whereas chronically elevated circulating IL-6 concentrations would induce insulin resistance in the liver and adipose tissue (Kim et al., 2009). The Panel notes that the human intervention study provided (de Bock et al., 2013) assessed differences in circulating IL-6 concentrations in blood samples obtained after a 12-hour fast following chronic (12-week) consumption of the olive leaf water extract, and thus such increase in IL-6 cannot be considered as “acute” or “localised” in the skeletal muscle. The Panel also notes that the role of IL-6 in carbohydrate metabolism is complex and still not well understood (Glund et al., 2008). Second, the applicant proposed that the olive leaf water extract (oleuropein and tannins) could decrease carbohydrate absorption by inhibiting α-glucosidase in the gut or salivary or intestinal α-amylase activity, or could stimulate hepatic glycogen synthesis, which

would result in "reduced hyperglycaemia". However, the study provided in support of that mechanism (Wainstein et al., 2012) was not conducted with oleuropein, tannins or the food that is the subject of the health claim. Third, the applicant suggested that the olive leaf water extract could exert the claim effect by increasing the activity of hepatic antioxidant enzymes via oleuropein and hydroxytyrosol (Jemai et al., 2009). The Panel notes that no evidence was provided that "lower activity" of hepatic antioxidant enzymes induces glucose intolerance in humans, or that consumption of the olive leaf water extract improves glucose tolerance by increasing the activity of hepatic antioxidant enzymes. The Panel considers that no evidence was provided by the applicant for a mechanism by which the olive leaf water extract could exert the claimed effect in humans.

In weighing the evidence, the Panel took into account that one human intervention study showed an increase in glucose tolerance without a disproportionate increase in insulin concentrations after daily consumption of the olive leaf water extract for 12 weeks under the conditions of use proposed by the applicant. However, the Panel also took into account that the results have not been replicated in other studies, and that the information supplied by the applicant did not provide evidence for a mechanism by which the olive leaf water extract could exert the claimed effect.

The Panel concludes that the scientific evidence is insufficient to establish a cause and effect relationship between the consumption of olive leaf water extract and an increase in glucose tolerance.

CONCLUSIONS

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

- The food, olive leaf (*Olea europaea* L.) water extract standardised by its content of oleuropein, is sufficiently characterised.
- The claimed effect proposed by the applicant is "reduces the glycaemic response following carbohydrate consumption". The target population proposed by the applicant is adults willing to reduce their glycaemic response. Increase in glucose tolerance is a beneficial physiological effect as long as serum insulin concentrations are not disproportionately increased.
- The scientific evidence is insufficient to establish a cause and effect relationship between the consumption of olive leaf water extract and increase in glucose tolerance.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on olive leaf water extract and increase in glucose tolerance pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0397_UK). September 2013. Submitted by Comvita New Zealand Limited.

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ABBREVIATIONS

AUC	area under the curve
BMI	body mass index
CRP	C-reacting protein
DXA	dual-energy X-ray absorptiometry
IGF	insulin-like growth factor
IGFBP	insulin-like growth factor growth factor-binding protein
IL	interleukin
IPAQ	International Physical Activity Questionnaire
ISI	insulin sensitivity index
OGTT	oral glucose tolerance test
OLE	olive leaf extract
SD	standard deviation
TNF	tumour necrosis factor