Anxiofit-1 and reduction of subthreshold and mild anxiety: evaluation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006 (Scientific Oplinion)

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)

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Anxiofit-1 and reduction of subthreshold and mild anxiety: evaluation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006

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Abstract

Following an application from Anxiofit Ltd. and ExtractumPharma Co Ltd., submitted for authorisation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of Hungary, 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 Anxiofit-1 and reduction of subthreshold and mild anxiety. The food, Anxiofit-1, *Echinacea angustifolia* root extract, standardised for the content of echinacoside (at least 3%) and the alkamide profile, which is the subject of the health claim, is sufficiently characterised. The Panel considers that reduction of subthreshold and mild anxiety is a beneficial physiological effect. Subthreshold and mild anxiety is a risk factor for anxiety and depressive disorders. One human intervention study with a small number of participants showed a decrease in anxiety scores under the conditions of use proposed by the applicant. Another small study, performed by the same research group with patients with diagnosed generalised anxiety disorder, also showed a decrease in anxiety in this population. However, the Panel notes that the results have not been replicated in other studies. The information supplied by the applicant did not provide evidence for a plausible mechanism by which Anxiofit-1 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 Anxiofit-1 and reduction of subthreshold and mild anxiety.

Keywords: Anxiofit-1, *Echinacea angustifolia*, anxiety, health claims

Requestor: Competent Authority of Hungary following an application by Anxiofit Ltd. and ExtractumPharma Co Ltd.

Question number: EFSA-Q-2015-00006

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Summary

Following an application from Anxiofit Ltd. and ExtractumPharma Co Ltd., submitted for authorisation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of Hungary, the European Food Safety Authority (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 Anxiofit-1 and reduction of subthreshold and mild anxiety.

The scope of the application was proposed to fall under a health claim referring to disease risk reduction.

The general approach of the NDA Panel for the evaluation of health claim applications is outlined in the EFSA general guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims.

The food that is the subject of the health claim is Anxiofit-1, *Echinacea angustifolia* root extract, standardised for the content of echinacoside (at least 3%) and the alkamide profile. The Panel considers that Anxiofit-1 is sufficiently characterised.

The claimed effect proposed by the applicant is 'amelioration of subthreshold and mild anxiety which are risk factors in the development of anxiety disorders and depression'. The target population proposed by the applicant is 'people having subthreshold and mild anxiety symptoms who are not eligible for anxiolytic medication'. The Panel considers that reduction of subthreshold and mild anxiety is a beneficial physiological effect. Subthreshold and mild anxiety is a risk factor for anxiety and depressive disorders.

The applicant provided three human intervention studies as being pertinent to the health claim.

In weighing the evidence, the Panel took into account that one human intervention study with a small number of participants showed a decrease of anxiety scores under the conditions of use proposed by the applicant. Another small study, performed by the same research group with patients with diagnosed generalised anxiety disorder, also showed a decrease of anxiety in this population. However, the Panel also took into account that the results have not been replicated in other studies. The information supplied by the applicant did not provide evidence for a plausible mechanism by which Anxiofit-1 could exert the claimed effect.

On the basis of data presented, the Panel concludes that the scientific evidence is insufficient to establish a cause and effect relationship between the consumption of Anxiofit-1 and reduction of subthreshold and mild anxiety.

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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, Articles from 14 to 17 of this Regulation lay down provisions for the authorisation and subsequent inclusion of reduction of disease risk claims and claims referring to children's development and health in a Community list of permitted claims.

According to Article 15 of this Regulation, an application for authorisation 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: Anxiofit-1 and amelioration of subthreshold and mild anxiety.

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of Anxiofit-1, a positive assessment of its safety, nor a decision on whether Anxiofit-1 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

2.1.1. Information provided by the applicant

Food as stated by the applicant

According to the applicant, the food for which a health claim is made is Anxiofit-1, a food supplement that contains 20 mg of an *Echinacea angustifolia* hydro-alcoholic root dry extract standardised for the specific alkamide profile.

Health relationship as claimed by the applicant

According to the applicant, the claimed effect is amelioration of subthreshold and mild anxiety which are risk factors in the development of anxiety disorders and depression.

Mechanism(s) by which the food/constituent exerts the claimed effect as proposed by the applicant

According to the applicant, Anxiofit-1 alleviates subthreshold and mild anxiety symptoms by its active principles called alkamides. The beneficial effects of Anxiofit-1 alkamides are mediated by interactions with the cannabinoid CB1 receptor, the fatty acid amide hydrolase (FAAH) enzyme that degrades the

[1] 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.

endocannabinoid anandamide in the brain and by an agonist action on the transient receptor potential vanilloid-1 (TRPV-1) receptor.

Wording of the health claim as proposed by the applicant

According to the applicant, Anxiofit-1 has been shown to ameliorate subthreshold and mild anxiety. Subthreshold and mild anxiety are risk factors in the development of anxiety disorders and depression.

Specific conditions of use as proposed by the applicant

According to the applicant, the quantity of *Echinacea angustifolia* root extract that should be consumed per day is 40 mg (20 mg should be consumed in the morning and 20 mg in the evening).

The target population proposed by the applicant are people having subthreshold and mild anxiety symptoms (not eligible for treatment with anxiolytic medications) but otherwise healthy.

Data provided by the applicant

Health claim application on 'Anxiofit-1' and amelioration of anxiety pursuant to Article 14 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 the evaluation of Article 13.1, 13.5 and 14 health claims (EFSA NDA Panel, 2011b), 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 claims applications is outlined in the EFSA general guidance for stakeholders on the evaluation of Article 13.5 and 14 health claims (EFSA NDA Panel, 2011b).[2]

The scientific requirements for health claims related to functions of the nervous system, including psychological functions are outlined in a specific EFSA guidance (EFSA NDA Panel, 2012).

3. Assessment

3.1. Characterisation of the food

The food that is the subject of the health claim is Anxiofit-1, *Echinacea angustifolia* root extract. This ethanol extract is standardised for the content of echinacoside (at least 3%) and the alkamide profile. The concentration of alkamides/echinacoside in the final food products is measured by high-performance liquid chromatography (HPLC). The alkamide profile of the product was presented in graphic form. Upon a request from EFSA, the applicant submitted data about total alkamide content (presented as the value of area under the HPLC peaks) and relative amounts of alkamide compounds in several batches of the product, and specified that subspecies of *Echinacea angustifolia* used in the product are *E. angustifolia* DC var. *angustifolia* and *E. angustifolia* DC var. *strigose*. The roots were collected in the USA.

Detailed specifications of the manufacturing process, stability information, bioavailability and batch-to-batch variability were provided by the applicant.

The Panel considers that the food Anxiofit-1, 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 'amelioration of subthreshold and mild anxiety which are risk factors in the development of anxiety disorders and depression'. The target population

[2] EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011. General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims. EFSA Journal 2011;9(4):2135, 24 pp. doi:10.2903/j.efsa.2011.2135

proposed by the applicant is people having subthreshold and mild anxiety symptoms who are not eligible for anxiolytic medication.

Upon a request from EFSA, the applicant clarified that subjects with subthreshold anxiety can be defined as subjects having symptoms of anxiety but not meeting the full diagnostic criteria for anxiety disorders in relation to the duration of symptoms or their number. The applicant also specified criteria used for the definition of mild anxiety: a score ≤ 17 in the Hamilton anxiety scale (HAM-A), a score of 8–10 in the hospital anxiety and depression scale – anxiety subscale (HADS-A), and a score of 45–57 points for subscales and 90–114 points for the total score in the state-trait anxiety inventory (STAI).

The applicant stated that the proposed diseases for the proposed risk factor include: anxiety disorders (particularly agoraphobia, generalised anxiety disorder, obsessive compulsive disorder, panic disorder, simple phobia and social phobia) and depressive disorders (particularly major depressive disorder, dysthymia, manic episodes and suicidality as symptoms of bipolar disorders).

Justifying the association between the proposed risk factor and disease the applicant submitted two types of evidence: observational studies showing increased risk of psychiatric disorders with the presence of the proposed risk factor and intervention studies documenting decreased risk of psychiatric disorders after decrease of the risk factor. Several studies showed the increased risk for a variety of psychiatric disorders including anxiety, panic disorder, depression, suicidality, bipolar disorder and depressive disorders in populations of subjects with subthreshold anxiety compared to healthy controls (Acaturk et al., 2009; Van't Veer-Tazelaar et al., 2009; Batelaan et al., 2010; Gallerani et al., 2010; Bystritsky et al., 2010; Karsten et al., 2011; Balázs et al., 2013). Two studies have shown that lowering the risk factor decreases the risk of disease. Aune and Stiles (2009) reported the results of a randomised clinical trial in which administration of the Norwegian Universal Preventive Program for Social Anxiety decreased social anxiety symptoms in older children and young adolescents with subthreshold social anxiety and also reduced the incidence of syndromal social anxiety. Van't Veer-Tazelaar et al. (2009) used a preventive stepped-care programme involving several forms of cognitive behaviour therapy administered in steps which reduced the development of anxiety and depressive disorders by 50% in an elderly sample with subthreshold symptoms of depression or anxiety.

The Panel considers that reduction of subthreshold and mild anxiety is a beneficial physiological effect. Subthreshold and mild anxiety is a risk factor for anxiety and depressive disorders.

3.3. Scientific substantiation of the claimed effect

3.3.1. Human studies

The applicant performed a literature search in PubMed database with the use of the following key words: Echinacea OR alkamides OR isobutylamides OR alkylamides AND anxiety OR anxiolytic. The search was limited to articles published in English. No date limits were set.

The applicant provided three human intervention studies as being pertinent to the health claim.

The unpublished study by Haller (2008) was a pilot one-arm open-label study assessing the effect of a commercially available ethyl alcoholic *Echinacea purpurea* root tincture (Dr. Theis Echinacea drops) on measures of state and trait anxiety in seven participants. The Panel considers that no conclusions can be drawn from this uncontrolled study, in which food other than food being the subject of the claim was used, for the scientific evaluation of the claim.

In a randomised, parallel, double-blind, dose-finding study Haller et al. (2013) evaluated the effects of tablets containing 20 mg of *Echinacea angustifolia* extract (Anxiofit-1). There were 33 participants (67% women, mean age 40.8 years) who had elevated STAI scores defined as greater than 45. Participants were excluded if they had any diagnosed Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) axis I disorder and/or psychotropic medication during the 6 months that preceded the study. Participants were randomly assigned to two groups which received either one or two tablets of *Echinacea angustifolia* extract per day for a period of seven days. STAI scores were obtained at baseline (days 1 and 3), and again on days 5, 6, 10, 17 and 24.

The effects of Anxiofit-1 on STAI scores were examined with repeated-measures ANOVAs with treatment and time as factors. Multiple comparisons underwent Bonferroni correction. Analysis of

main effects was not reported, but there was a significant treatment x time interaction ($F(6,180) = 4.91$; $p < 0.0002$). STAI scores for the 20 mg/day group showed no significant changes across the duration of the study, but scores for the 40 mg/day group were significantly reduced by day 6 compared to baseline and remained significantly reduced for the remainder of the study. However, no comparisons of STAI scores between the treatment groups were reported. Upon a request from EFSA, the applicant submitted additional pairwise comparisons between the groups showing that both State Anxiety scores (20 mg/day: M = 60.60, SEM = 1.20; 40 mg/day: M = 50.2, SEM = 2.14, p = 0.013) and Trait Anxiety scores (20 mg/day: M = 59.47, SEM = 1.08; 40 mg/day: M =50.88, SEM = 1.76, p = 0.025) were statistically different at the seventh day of the intervention, and STAI total scores were statistically different between both groups at both the third day (20 mg/day: M = 120.87, SEM = 1.85; 40 mg/day: M = 105.65, SEM = 4.17, p = 0.040) and seventh day (20 mg/day: M = 120.07, SEM = 2.12; 40 mg/day: M = 50.2, SEM = 3.68, p = 0.009) of the intervention. All comparisons underwent Bonferroni correction for multiple comparisons. The Panel considers that this study showed that Anxiofit-1 in a dose 40 mg/day decreases anxiety measured by STAI State Anxiety, Trait Anxiety and total score.

The third human study submitted was performed by the same group of investigators (Haller, 2013, unpublished). There were 26 participants (73% women, mean age 43.2 years) with a diagnosis of generalised anxiety disorder (GAD) according to DSM-4 criteria, a HAM-A score between 17 and 25 points at the screening and randomisation visits (indicating mild to moderate anxiety severity), and a total Beck depression inventory (BDI) score lower than 10 (indicating minimal depression). Participants were excluded if they had any anxiety disorder other than generalised anxiety, any depressive disorder, anorexia, bulimia, alcohol or substance abuse or dependence, schizophrenia, antisocial or borderline personality disorder, with serious suicidal risk, participated in psychotherapy and taking currently psychotropic medications were excluded. The design was a randomised, two-arms, placebo-controlled, double-blind, multicentre study. The Panel notes that the study population were patients with a diagnosis of GAD according to DSM-4 criteria, and not the target population which is the subject of the claim. Upon a request from EFSA related to possibility of extrapolation of the results of this study to the target population, the applicant stated that subthreshold and clinical-level GAD should not be treated as 'radically different conditions', that other anxiolytics developed to reduce GAD symptoms have also been found to reduce subthreshold symptoms, that the majority of patients with GAD do not seek medical help, and that patients with anxiety and depression prefer to use food additives in preference to conventional therapies.

After 3 days run-in period, the subjects were given Anxiofit-1 (40 mg/day) or placebo for 6 weeks. Anxiety levels were assessed by the HAM-A scale on four occasions (screening, randomisation, and days 14 and 42) and the HADS–A on eight occasions (screening, randomisation, and days 2, 7, 14, 16, 28 and 42).

Two-factor ANOVA tests were used in the statistical analysis of the results (factor 1: Anxiofit-1 consumption; Factor 2: time from randomisation). HAM-A scores decreased significantly over time, but there were no significant differences between the Anxiofit-1 and placebo groups. The Panel notes that the HAM-A scale, which was developed more than 50 years ago, is now considered to be an inadequate outcome measure because it poorly discriminates between generalised anxiety disorder and depression (Koerner et al., 2010). HADS–A scores were significantly lower for the Anxiofit-1 group compared to placebo ($F(1, 142) = 12.35$; $p = 0.0006$) and there was no significant interaction with time. The effect of Anxiofit-1 first appeared on day 2 of treatment and remained unchanged for the duration of the study.

The Panel considers that this study shows an effect of Anxiofit-1 on anxiety in a group of patients with diagnosed GAD.

3.3.2. Mechanism of action

The applicant indicated that the mechanisms by which Anxiofit-1 could exert an effect on anxiety are probably complex and mainly related to the presence of alkamides, which can activate molecular and brain mechanisms involved in anxiety control. Alkamides can act as cannabinomimetics at both the cannabinoid CB1 and CB2 receptors, and can also inhibit the anandamide-degrading enzyme fatty acid amid hydrolase (FAAH) (Haller et al., 2010). To support this effect, the applicant provided an *in vitro* study (Woelkart et al., 2005) which showed that alkamides from *Echinacea angustifolia* roots bind to

both the CB1 (on rat brain membranes) and CB2 (rat spleen membranes) cannabinoid receptors. In another *in vitro* study performed on rat brain membrane preparations, Hohmann et al. (2011) showed that the G-protein modulating effect of alkamides from *Echinacea* root extract on CB1 receptors was weaker than the effect of the synthetic full agonist, but a number of alkamides were able to inhibit the stimulation of the pure agonist, indicating cannabinoid receptor agonist properties. The applicant also proposed that some *Echinacea* alkamides inhibit the enzyme FAAH that degrades the endocannabinoid anandamide in the brain, which may increase endocannabinoid signalling. In an *in vitro* study, Woelkart et al. (2005) found that this activity was shown by three *Echinacea* alkamides, one of which is present in Anxiofit-1. The applicant also suggested that as yet unidentified constituents of *Echinacea* extracts may activate TRPV1 receptors, which are involved in peripheral pain reception and probably in the regulation of affective behaviours. To support this notion, the applicant submitted an *in vitro* study (Birt et al., 2008) showing that *Echinacea* extract evoked an ion current 10-fold greater than a saturating dose of capsaicin, a ligand of TRPV-1 receptors. Finally, the applicant noted the role of the hippocampus in anxiety, and presented a study showing that *Echinacea angustifolia* root extracts regulated excitatory, but not inhibitory, synaptic transmission of rat hippocampal neurones which might explain the anxiolytic effects (Hajos, 2012). The Panel notes that it was not documented that alkamides from *Echinacea* cross blood–brain barrier or can be present in the brain after oral intake, although one *in vivo* study in rats reported a rapid passage of the main alkamides in *Echinacea* across the blood–brain barrier (Woelkart et al., 2009).

The Panel notes that the activation of cannabinoid receptors is not specific for anxiety and depression treatment and may play a role in many different clinical situations (Pertwee, 2012), and that the activation of CB1 receptors by cannabinoids may lead to the down-regulation of the endocannabinoid signalling system, producing a worsening of anxiety-related disorders (Neumeister, 2013; Korem et al., 2015). The Panel also notes that the evidence for the role of cannabinoid receptors on anxiety disorders comes mainly from preclinical studies and was not confirmed in human studies (Neumeister, 2013; Korem et al., 2015).

The Panel considers that the evidence provided by the applicant for the mechanisms by which Anxiofit-1 could exert an effect on anxiety is mostly speculative. The Panel considers that no evidence has been provided by the applicant for a mechanism by which Anxiofit-1 could exert the claimed effect *in vivo* in humans.

3.3.3. Weighing of the evidence

In weighing the evidence, the Panel took into account that one human intervention study in 33 participants showed a decrease of anxiety scores under the conditions of use proposed by the applicant. Another study in 26 participants, performed by the same research group with patients with diagnosed GAD, also showed a decrease of anxiety in this population. However, the Panel also took into account that the results have not been replicated in other studies. The information supplied by the applicant did not provide evidence for a plausible mechanism by which Anxiofit-1 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 Anxiofit-1 and reduction of subthreshold and mild anxiety.

4. Conclusions

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

- The food, Anxiofit-1, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect proposed by the applicant is 'amelioration of subthreshold and mild anxiety'. The target population proposed by the applicant is the general population. Reduction of subthreshold and mild anxiety is a beneficial physiological effect. Subthreshold and mild anxiety is a risk factor for anxiety and depressive disorders.
- The scientific evidence is insufficient to establish a cause and effect relationship between the consumption of Anxiofit-1 and reduction of subthreshold and mild anxiety.

Documentation provided to EFSA

1. Health claim application on Anxiofit-1 and 'reduction of subthreshold and mild anxiety' pursuant to Article 14 of Regulation (EC) No 1924/2006 (Claim serial No: 0432_HU). Submitted by Anxiofit Ltd, 1131 Budapest, 2 Szomszed Str, Hungary and ExtractumPharma Pharmaceutical Manufacturing, Marketing and Servicing Co. Ltd., 1044 Budapest, 64 Megyeri Str, Hungary.

2. This application was received by EFSA on 05/01/2015.

3. The scope of the application was proposed to fall under a health claim referring to disease risk reduction.

4. On 21/01/2015, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.

5. On 13/03/2015, EFSA received the missing information as submitted by the applicant.

6. The scientific evaluation procedure started on 18/03/2015.

7. On 6/05/2015, 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 stopped on 12/05/2015 in compliance with Article 18(3) of Regulation (EC) No 1924/2006.

8. On 25/06/2015, EFSA received the requested information and the scientific evaluation was restarted.

9. On 10/09/2015, 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 stopped on 15/09/2015 in compliance with Article 18(3) of Regulation (EC) No 1924/2006.

10. On 09/10/2015, EFSA received the requested information and the scientific evaluation was restarted.

11. During its meeting on 10/12/2015, the NDA Panel, having evaluated the data, adopted an opinion on the scientific substantiation of a health claim related to Anxiofit-1 and reduction of subthreshold and mild anxiety.

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Abbreviations

ANOVA	analysis of variance
BDI	Beck depression inventory
CB	cannabinoid
DSM	diagnostic and statistical manual of mental disorders
FAAH	fatty acid amide hydrolase
GAD	generalised anxiety disorder
HADS-A	hospital anxiety and depression scale – anxiety subscale
HAM-A	Hamilton anxiety inventory
HPLC	high-performance liquid chromatography
STAI	state-trait anxiety inventory
PSS	perceived stress scale
TRPV	transient receptor potential vanilloid