European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT ON

AVENA SATIVA L., HERBA AND *AVENA SATIVA* L., FRUCTUS

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

I. REGULATORY STATUS OVERVIEW[1]

MA: Marketing Authorisation;
TRAD: Traditional Use Registration;
Other TRAD: Other national Traditional systems of registration;
Other: If known, it should be specified or otherwise add 'Not Known'

Member State	Regulatory Status				Comments[2]
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
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Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
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Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

[1] This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.
[2] Not mandatory field

Assessment Report

Botanical species and variety	***Avena sativa* L.**
Botanical family	**Poaceae - Gramineae**

Botanical synonyms

Avena orientalis Schreb., *Avena chinensis* (Fisch.) Döll.

Part of the plant	**Fructus Avenae** **Herba Avenae**
Pharmaceutical preparations	**Herbal substance or herbal preparations in solid or liquid dosage forms**
Rapporteurs	**Prof. Gert Laekeman** **Prof. Arnold Vlietinck**

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I. INTRODUCTION

This assessment report reviews the available scientific data for *Avena sativa* herba and *Avena sativa* fructus.

In preparing this report, a number of data sources have been taken into account. The main ones are as follows:

- The results of a literature search carried out using the available references in PubMed (last observation April 2007).
- The Cochrane database (last observation June 2007)
- Monographs included in the reference list.
- Standard books on phytotherapy.
- Internet sites on 'Avena', 'phytotherapy' and specific therapeutic applications.

The plant is used for its fruits and also herb, harvested before flowering (Hänsel et al. 1992). In addition, some authors refer to use of the fresh plant just before harvest (Anand 1971; Bye et al. 1974).

II. PHARMACOLOGY

II.1. Phyto-chemical characterization

II. 1.1. *Avena sativa* fruits

Several fractions and substances have been described for the fruits of oats (Daniels & Martin 1967, List & Hörhammer 1972, Lasztity 1984, Krug 1985, Schneider 1985, Frølich & Nyman, 1988, Nie et al. 2005; Bratt et al. 2003, Bryngelsson et al. 2002).

Sugar fraction: mucilage (beta-glucan); 3 to 4% sugar (fructose, glucose),

Protein fraction: contains glutelin (> 50%) and avenin . The globulin of oats fruits could be separated into an acidic (32,500 - 37,500 Dalton) and a basic part (22,000 - 24,000 Dalton). The unreduced protein exists as disulfide-linked alpha/beta species of molecular weight 53,000 to 58,000. There is a considerable heterogeneity within both groups of polypeptides (Brinegar & Peterson, 1982). The protein fraction of oats contains more lysine as compared to other cereals. Endosperm, hulls (outer shells), embryonic axis and scutellum are rich in glutamic acid.
Various enzymes were identified, including alpha-amylase, phosphatase, tyrosinase, maltase and lipase. From a practical point of view the lipases are the most important. Hydrolysis of the triglycerides is undesirable, due to the soapy and bitter flavours which can result.

Lipid fraction: the grains of oats contain the highest lipid fraction among all feeding crops belonging to the family of the Poaceae. Unsaturated hydroxy fatty acids are formed by lipid peroxidase activity. Avenothionin was identified as a viscotoxin-like purothionin low molecular weight lipoprotein. It could be separated into alpha and beta avenothionin, of which the former had 47 amino acids.

Alkaloids: The indole alkaloid gramine is thought to be responsible for a weak sedative effect similar to *Passiflora.*

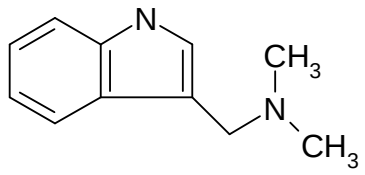
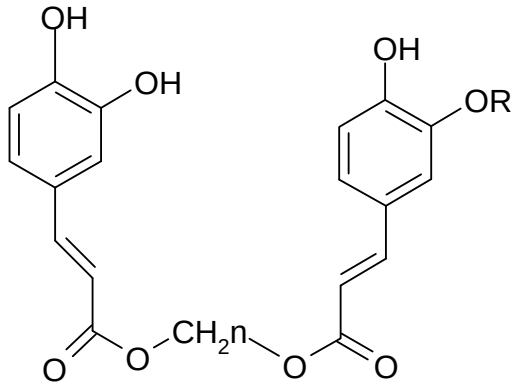


Figure 1: the alkaloid gramine

Organic acids: Diverse organic acids: malic, citric, malonic, aconitic, oxalic acid: (the latter up to 0.04%). Caffeic and ferulic acid have antioxidant properties. Avenanthramides are described as polyphenols in oats seeds. The latter represents a group of phenolic compounds which are not present in other cereal grains. Steaming and flaking of dehulled oat groats (inner kernel) resulted in moderate losses of avenanthramide Bp, while ferulic acid and vanillin increased. Avenanthramides Bc and Bf were not affected by steaming.



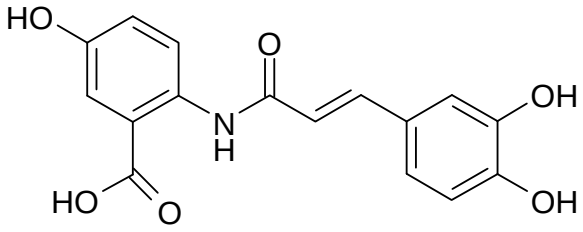


Figure 2: left: phenolic antioxidant, hydrolysed in equimolar proportions of caffeic acid, ferulic acid and an aliphatic alcohol (R = Me or H). Figure 3 Right: avenanthramide-2c.

Figure 3: Vanillosid, a vanillin glycoside, reported to make the aroma *of the seeds attractive to horses.*

The burned cinders (as) reported to contain 50 to 70% silicon dioxide (SiO2**)**.

Flavonoids: To date, 28 flavonoids have been identified in the seeds and the green parts of the plant. Rhamnosylisoswertisin may have phytoalexin properties, protecting the plant against mycoses. Also 3 flavonolignanes derived from the flavone, triticin, were isolated from *Avena sativa* herb. Figure 4. In the known compounds a coniferyl alcohol moiety is linked to the flavone by an ether bond. In a new natural product, it is linked by C-C bonds (Wenzig et al. 2005).

Saponins may also protect oats against fungal infections. They are of the triterpene saponin type.
Steroids in the seeds like avenasterin and stigmasterin.

Vitamins: The seeds contain vitamins as indicated in the table below.

Table 1: Vitamin content of oats

Vitamin	content	reference
Vitamin A	0.862 mg/100g (mucilage)	Bognar 1986
Beta-carotene	< 1.0µg/100g ('rolled' oats)	Heinoven et al. 1989
Vitamin B1 / thiamine	3.89-7.07 mg/kg	Jahn-Deesbach, 1979
Vitamin B6	56 nmol/g	Gregory & Sartain, 1991
Vitamin E / tocopherol	4,3 (alpha-T) – 0.5-1.0 (beta-T)	Barnes & Taylor, 1981

Cyanoglycosides: Sprouts can contain the cyanoglycoside linamarin. The content declines during the development of the plant (two leaves stadium only 10µM/100g).

Green oats contain mainly pectin and SiO_2, esters with polyphenols and mono- or oligosaccharides. These oligosaccharides can be incorporated in cellulose, facilitating the fixation of minerals. This fixation can have negative effects, described as for instance the rachitogenic factor when calcium is fixed in phytinic acid complexes from which dissociation is difficult. Fixation is also reported for phosphates.

II. 1.2. *Avena sativa* green herb harvested before flowering

The composition of this part of the plant is described by Hänsel et al. (1992).

Sugar fraction: beta-glucan, pentosans, saccharose, kestose, neokestose, bifurcose, neobifurcose and the acid galactoarabinoxylan.

N-containing carboxylic acids: avenic acid A and B.

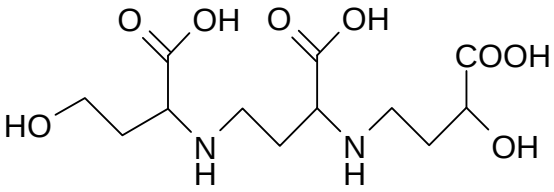


Figure 4: Avenic acid A

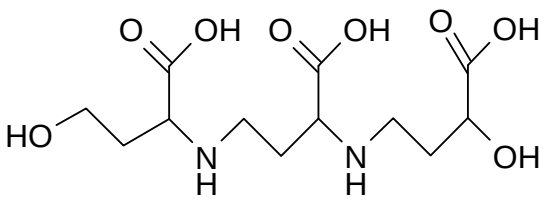


Figure 6: Avenic acid B

Saponins: avenacoside A and B. These are glycosylated steroidal saponins. Leaves contain furostanol saponins. Avenacosid content of leaves varies between 1-3 mg/g.

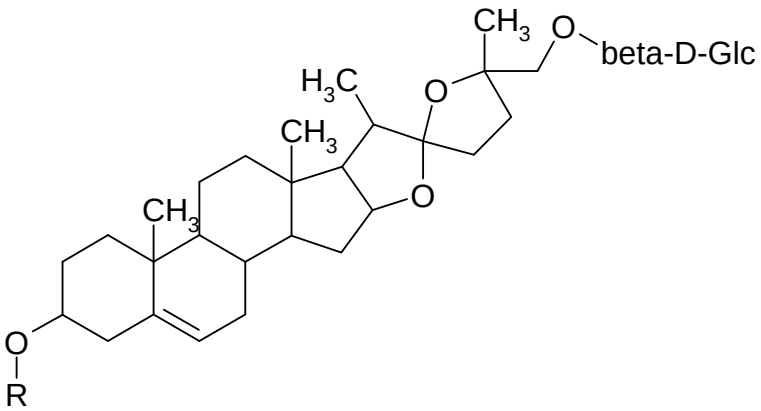


Figure 5: Avenacoside A and Avenacoside B.
Avenacoside A : R = βDGlc-[(4-1)Rha]-[(2-1)βDGlc]
Avenacoside B : R= βDGlc-[(4-1)Rha]-[(2-1)βDGlc-(3-1)βDGlc]

Flavonoids: e.g. vitexin derivatives. See above under oat fruit.

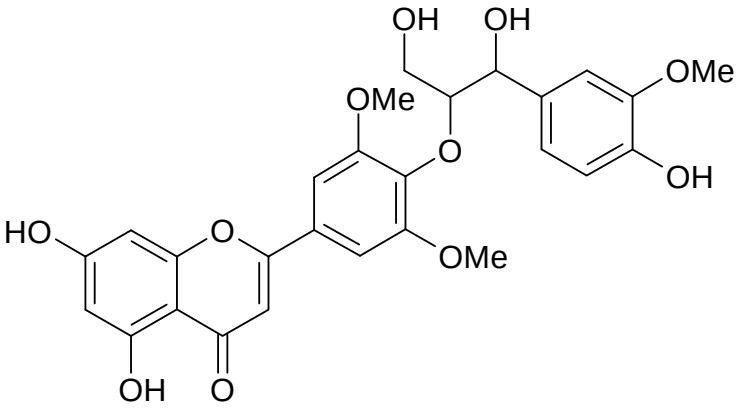


Figure 6: tricin derivatives isolated from Avena sativa herb.

Mineral substances: see Table 2.

Table 2: Mineral content of fruits and green parts of *Avena sativa* (oats) (mg/100g)

	Oats seeds	Green oats
K	355	1140
Ca	79.6	660
Mg	129	715
P	342	330
Mn	3.7	8.5
Fe	5.8	39
Zn	4.5	19.2
Cu	0.47	2.1

II.2 Absorption, metabolism and excretion

Bioavailability of avenanthramides, extracted from hull-less oats, was tested in hamsters. The avenanthramides were extracted with an ethanol: water (80:20) mixture and characterised with HPLC. Plasma levels were also detected with HPLC after oral gavage. Peak plasma concentrations were obtained after 40 minutes. Apparent relative bioavailability was limited to 1.3% for both avenanthramide A and B (using 2',3',4'-trihydroxyacetophenone as an internal standard). Ferulic acid had a bioavailability of 49.5% (Chen et al. 2004).

II.3. Pharmacodynamics

Schneider (1985) gives an overview of pharmacological activities described in the literature. Most of the references are difficult to access (thesis, patents or poorly referenced documents).

Table 3: Overview of literature data regarding pharmacological activities of *Avena sativa*

Activity	Plant part / substance
Antibiotic effect (*in vitro*): fungi < 3µg/ml; Mycobacterium < 12.5µg/ml	Saponins: avenacin, avenacosid
Antagonism of morphine (mice) Antagonism of hypertensive effect caused by nicotin (rats)	Alcoholic (90%) extract of green oats
Inhibition of prostaglandin synthesis	Seeds extract with phosphate buffer and alcohol (96%)
Smoking cessation	Alcoholic extracts (90%) of the aerial parts
Cholesterol lowering effect	Steroids
Inhibition of plaque formation of teeth	Polysaccharides from the seeds outer wall
Inhibition of protein synthesis	Protein fraction
Lowering uric acid serum levels	Tea of green oats
Rachitis	Phytic acid in fruits

Enhancing FSH	Extract of leaves
Stimulating LH-formation	Leaves
Anti-estrogenic effects	Dried herb
Protection against gastro-intestinal ulcera	Polyphenols

In vitro

Inhibitory activity on MAO-B

Extracts of *Avena sativa* herb, made with different ethanol concentrations were tested in an *in vitro* model. A commercially available enzyme preparation of MAO-B was used in a one-step fluorimetric method in microtiter plates. The assay is based on the detection of H_2O_2 in a horseradish peroxidase-coupled reaction usinf N-acetyl-3,7-dihydroxyphenoxazine (Amplex red) (Zhou & Panchuk-Voloshina, 1997).
More prominent inhibitions were obtained when the extracts were prepared with higher concentrations of ethanol (mean + SD):

- 15% ethanol: 44.3 + 1.4 % inhibition
- 30% ethanol: 57.2 + 0.8% inhibition
- 50% ethanol: 78.6 + 0.4% inhibition

These data were transmitted on file and no further details on the way the extracts were prepared and the way solvent controls were incorporated were given (Frutarom, data on file 2008). Also the number of assays per extract was not transmitted. MAO-B inhibitors are used in Parkinson's disease (e.g. rasagiline and selegiline). From the data transmitted it is not clear whether the inhibition was selective for MAO-B, as no data for MAO-A were communicated.

Inhibitory activity on PDE-4 activity

The same extracts (see '*Inhibitory activity on MAO-B*') were tested on phosphodiesterase-4 (PDE-4). The tests were done with an undifferentiated U937 human monocytic cell line. This cell line enabled to test the hormonal regulation of the c-AMP. The c-AMP content could be temporarily increased by adding the beta-agonists and salbutamol (cf. stimulation of adenylcyclase), followed by an increase in PDE. PDE decreases the content of c-AMP by converting c-AMP to AMP. Inhibtion of PDE will result in increased intracellular c-AMP levels. Residual c-AMP was quantitatively assessed by measuring the radioactivity corresponding with [^{3}H]cAMP after separation by ion exchange column chromatography (Torphy et al. 1992).
Extracts prepared with higher concentrations of ethanol gave higher inhibitions of the PDE-4 activity (mean $\pm$ SD):

- 15% ethanol: 35.3 $\pm$ 3.3% inhibition
- 30% ethanol: 66.5 $\pm$ 1.2% inhibition
- 50% ethanol: 89.5 $\pm$ 2.4% inhibition

These data were transmitted on file and no further details on the way the extracts were prepared, the number of assays and the way solvent controls were incorporated were given (Frutarom, data on file 2008). Inhibition of PDE-4 will result in higher intracellular c-AMP levels and can influence neurotransmission. As from *in vitro* results it is very difficult to make any extrapolation to possible effects *in vivo*.

Assessor's comments
Both series of experiments open interesting perspectives as a neurogenic activity of *Avena sativa* is concerned. As these preliminary data are on company file, more work has to be done in order to gain insight in the mechanisms of action exerted by *Avena sativa* extracts. None of the results has been published in peer reviewed journals up to now.

Anti-atherogenic activity

Avenanthramide-2c, a polyphenol from oat fruits, inhibits vascular smooth muscle cell proliferation and enhances nitric oxide production. There was a concentration dependent inhibition of the incorporation of ^{3}H thymidine in human vascular smooth muscle cells. Concentrations varied between 40 and 120 µM. The effect was seen as an inhibition of proliferation of the vascular smooth muscle. Also the number of viable smooth muscle cells was significantly lowered ($P < 0.05$). The inhibition was reversible after washing out aventhramide-2c. Same concentrations of the compound stimulated the synthesis of NO in a human endothelial cell line ($P < 0.05$) (Nie et al. 2005).

The potential antiatherogenic activity of partially purified avenanthramides from oats was tested by evaluating their effects on adhesion of monocytes to human aortic endothelial cell monolayers, expression of adhesion molecules and production of proinflammatory cytokines and chemokines by the endothelial cells. The avenanthramides were prepared by refluxing and purified by column chromatography. The pre-incubation of HAEC with 4, 20 and 40 ng/ml avenanthramide enriched mixture (AEM) for 24 hours significantly decreased adhesion of U937 monocytic cells to interleukin-1beta-stimulated HAEC. The inhibition was concentration dependent. Pre-incubation of HAEC with EAM at 20 and 40 µg/ml, but not at 4 µg/ml, for 24 hours significantly suppressed IL-1beta-stimulated expressions of intracellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectine and the secretion of proinflammatory cytokines IL-6, chemokines IL-8 and monocyte chemoattractant protein (MCP)-1 (Liu et al. 2004).

There was a concentration-dependent increase in lag time for Cu^{++}-induced oxidation after addition of oat phenolics to human LDL *in vitro* (0.52 to 1.95 µM). Ascorbic acid (2.5 and 5 µM) added to the oat phenolics synergistically extended the lag time for oxidation. The phenolics were extracted with ethanol:water (80:20 v/v) (Chen et al. 2004). In general, avenanthramides showed a higher antioxidant level than each of the following typical cereal components: ferulic acid, gentisic acid, p-hydroxybenzoic acid, protocatechuic acid, syringic acid, vanillic acid, vanillin and phytic acid. When the antioxidant capacity during 28 days of storage was measured by the linoleic acid assay, oat samples showed a very good antioxidant activity (Martinez-Tome et al. 2004).

Assessor's comments
The recent investigations described above have mainly been carried out using secondary metabolites isolated from fruits. They cannot be considered as directly linked to the traditional uses of *Avena sativa*. Further *in vivo* clinical investigation needs to be undertaken.

Topical anti-inflammatory activity

Vasoactive intestinal peptide (VIP) was used as trigger to cause inflammation in human skin cell culture. Vasodilation was significantly increased after application of VIP. After treatment with oatmeal extract oligomer, the mean surface of dilated vessels and edema were significantly decreased. Moreover, treatment with this extract decreased TNF-alpha (Boisnic et al. 2003).

The same author tested a spray containing Rhealba oat extract on human skin fibroblasts. Then a punch biopsy as a source of epidermal cells was implanted on this dermal equivalent, where a multilayered epidermis developed. Epidermal growth was evaluated by immunohistochemical analysis of mitotic activity (5-bromo-2'-deoxyuridine [BrDu] incorporation). The extension of the neoepithelium in comparison with untreated reconstituted skin over 22 days was evaluated histologically. On day 12, 16% of positive BrDu basal cells was detected after spray treatment in comparison with 4.2% positive cells in untreated reconstituted skin ($p < 0.05$). During epidermal differentiation between days 12 and 22, a significant increase in the number of cellular epithelial layers after 16 and 18 days of spray treatment was seen. Moreover the extension of re-epithelialization was also significantly increased after spray treatment on days 16 and 18 (Boisnic 2005).

Aries et al. (2003 and 2005) found an inhibition by a colloidal extract of *Avena sativa* (Avena Rhealba®) of the Ca-ionophore A23187 on the liberation of arachidonic acid from phospholipids and the subsequent metabolism into prostaglandins and leukotrienes. The inhibition of the biosynthesis of

prostacyclin (measured as 6-ketoPGF$_{1\alpha}$) was dose dependent. Also the expression of phospholipase and COX-2 was tempered. These findings open some perspective as anti-inflammatory activity in the skin is concerned.

Cytokines represent a large series of regulatory proteins of the immunologic system. They are produced by cutaneous cells during inflammatory processes. Examples are interleukins (e.g. IL2, IL4, IL5 and IL13) produced in atopic conditions, contact eczema and psoriasis. A colloidal extract of Avena stimulated the production of the anti-inflammatory TGFβ1 by keratinocytes and inhibited the production of interleukins (Aries et al. 1999a).

During cutaneous inflammation processes the neuro-immunocutaneous system is destabilized. More particularly an enhanced production of neurologic mediators such as substance P and consequently nitric oxide (NO) is seen. The substance P mediated stimulation of NO synthesis is blocked by an Avena flour preparation. An inhibition of the expression of NO-synthase is identified as basic mechanism (Aries, 2000).

Aries (1999b) studied the activity of Avena flour preparations on an experimental wound healing model. The expression of the Vascular Endothelial Growth Factor (VEGF) by human keratinocytes in the Boyden chamber was induced and augmented the migration of keratinocytes and collagen fibre contraction.

Assessor's comments
These *in vitro* investigations are indicative of an anti-inflammatory activity of several oat fruit preparations. The results can be considered to support the plausibility of the traditional topical use of *Avena sativa* for dermatological conditions.

In vivo

Neurological activities

Non specific effects on brain activity were investigated after oral administration of Neuravena® (EFLA®955 = standardised wild green oat extract, Frutarom Industries Ltd) to rats (quantitative information on the dose administered was not given). Oral gavage was continued over a 90 minute period. EEG was recorded during 5 hours using the 'Tele-Stereo EEG' methodology. The brain pattern obtained were suggestive stimulation of dopaminergic neurotransmission implicated in cognitive functioning, motivation and depression. The results were in accordance with previously *in vitro* seen MAO-B inhibitory activity (Frutarom data on file).

The effect of Neuravena® was also studied in behavioural trials. A group of 12 rats was administered a dose of 1g/kg body weight with their food over a period of 7 weeks. Another group received a tenfold dose and a control group received a normal diet. The results indicated enhanced stress coping abilities and alertness as well as improvement in general learning performance and speed of learning. Moreover, a positive effect on social behaviour was observed. A subsequent pathological examination also confirmed that Neuravena® was well tolerated in this subchronic treatment (Frutarom data on file).

Assessor's comments
To our knowledge the study of these neurological effects are a first approach to the traditional use of *Avena sativa* herb in different conditions related to stress. More investigations are welcomed and the publication in peer reviewed journals of the data mentioned above are highly recommended.

Avena sativa and *Amaranthus hypochondriacus* were used in a comparative study. Antioxidant compounds were compared in both species (2 varieties of the latter were studied). Polyphenols, anthocyanins, flavonoids and beta-carotene were present in higher concentrations in Avena as compared to the Amaranthus species. Rats were fed with a basal diet or with basal diet to which 1% cholesterol was added. The cholesterol fed rats received additionally 10% oats meal or 10% amaranth.

Each experimental group consisted of 12 rats. Avena as well as amaranth kept cholesterol, LDL-cholesterol and triglycerides lower as compared to the cholesterol-only group. HDL-cholesterol was higher in the experimental groups as compared to the cholesterol-only group. The differences were significant and more outspoken for oats ($P < 0.001$) than for amaranth ($P < 0.05$) (Czerwinski et al. 2004).

The oral or parenteral oat beta-glucan treatment enhanced the resistance to *S. aureus* and *E. vermiformis* infection in mice. Beta-glucan increased the number of splenic IFN-γ-secreting cells and induced a change in the lymphocyte population (Thy1.2+, CD4+, CD8) in the mesenteric lymph nodes (Yun C.-H. et al. 2003).

The cholesterol lowering potency of beta-glucan (2, 4 or 8 g/100g; n=8-9 per group) is comparable to that of barley in Syrian golden F_1B hamsters fed with a cholesterol rich diet during 9 weeks (Delaney et al. 2003).

Assessor's comments
These *in vivo* experiments are partially useful in the development of well established use indications. They should be coordinated with clinical trials preferentially done with standardised preparations of oats seeds.

III. CLINICAL EFFICACY

III.1 Dosage

The following preparations have been used as traditional herbal medicines:

- The mucilage of oat fruits is traditionally used without specification of an exact dose.

Systemic use

- Tincture of *Avena sativa* fresh herb: 3x 40 drops per day are recommended (Van Hellemont 1985).

- Tincture of Avena is also mentioned by Madaus (1938), without any further specification. Most probably it is made from Avena herb as most of the indications are referring to the central nervous system.

- The 'Urtinktur' (mother tincture) is made of fresh seeds (1/10) 100g, water 233 ml and alcohol 94.9 vol.% ad 1000ml. No dose is specified (List & Hörhammer, 1972).

- The British Herbal Pharmacopoeia recommends a liquid extract of the seeds (1:1) in 25% alcohol: 0.6-2ml; and a tincture (1:5) in 45% alcohol: 0.2-5ml (Anonymus, 1976; Hänsel et al. 1992).

- The mother tincture of the fresh herb as described in HAB34 is mentioned (Schneider 1985).

- In Germany a preparation called 'Schoeneberger naturreiner Heilpflanzensaft Hafer' is available (Anonymus 2008)

- According to some sources homeopathic preparations with the same tincture in potencies from D3 to D200 can be used: 5-6 drops mixed with a spoonful of water can be used every half hour in case of acute symptoms. Children between 6-12 years can use half of this dose (Anonymous 2007).

- Of the herb harvested before flowering, one teaspoon (± 3g) is mixed with 250ml boiling water. After cooling, the water is sieved from the mixture and taken several times a day as well as before sleeping (Hänsel et al. 1992).

- When used to influence smoking habits, *Avena sativa* fresh plant was selected just before harvest: 1.5 parts of the crushed whole (weight) plant in 5 parts of 90% ethyl alcohol (volume) kept at room temperature with frequent agitation for 72 hours and then filtered. Of this filtrate, 1ml was diluted with 4ml of water and this preparation was taken 4 times a day (Anand, 1971; Bye et al. 1974).

Cutaneous use

- For a bath of 150 to 200 litres, 60g Avena flour is prescribed; for children 50% of this dose is used.

- Preparations of Avena seed flour are used. Colloidal extracts of flour are incorporated in a vehicle (e.g. petrolatume) in a concentration up to 20 to 30%.

- 'Aveeno®' products contain the colloidal extract in different forms:
  - 'Aveeno-bar®': soap containing at least 50% of pure colloidal oatmeal.
  - 'Aveeno oatmeal®': to be added to water for bathing.
  - 'Aveeno oilated®': nonsensitising protective oil added to the oatmeal.
  - 'Aveeno ointment®': Lassar paste with the starch component replaced by colloidal oatmeal.

- Liquid paraffin with 5% oatmeal was used to treat burns.

- Mostly fruits of Avena sativa are prepared as 'colloidal oatmeal' described in the USP 30 (1990). It consists of the powder obtained by grinding the whole fruits, resulting in oat flour and mixed with water. Viscosity, limits of microbial contamination, water content, particle diameter and ash composition are specified.

III.2 Clinical studies

Clinical trials

Open trials

Effect on uric acid excretion

Two studies have been conducted with a combination herbal product. There are no studies with Avena preparations as a single component.

A group of 51 patients with elevated uric acid levels was treated with a tea formula containing *Avena sativa* (green oats 75%), *Urtica dioica* (herba 10%), *Hypericum perforatum* (herba 10%) and *Alchemilla alpine* (herba 5%). The treatment period was 4 (n=21; mean age 58) or 8 (n=30; mean age 39) weeks. The posology was not reported. In both groups serum uric acid levels were lower at the end of the treatment periods as compared to the initial levels: 8.87mg% versus 7.09mg% and 9.31mg% versus 6;45mg% respectively (Krug 1985).

The same tea formula was compared in an open cross-over study with mineral water. Patients (n=20) with asymptomatic hyperuricemia (6.5 to 10 mg%) were included. Patients took 6 cups of tea or 6 glasses of water additionally to the normal fluid intake. Treatment duration was 20 days. There was one week wash-out period between both regimens. Purines were restricted during the study period. Uric acid levels were lowered in both groups. The difference between treatment and controls did not reach significance (P = 0.066) (Drisch 1988).

Cutaneous use

Studies with single component oat preparations:

The effects of colloidal oatmeal derivates in daily use of some products for skin care on 300 children. After 3 months of treatment the cutaneous conditions improved according to the physicians in 201/263 children. Parents increased satisfaction level during the study as their judgement regarding the products was "very good" in 153/263 cases after 2 weeks of treatment and in 201/263 cases after 3 months (Camplone et al. 2004).

Treatment with colloidal oatmeal was applied to 11 patients with a rash induced by cetuximab, erlotinib, panitumumab and sorafenib. Of the 10 assessable patients, 6 had complete response and 4 partial responses, with no associated toxicities. Treatment with colloidal oatmeal lotion was considered to be effective in controlling the rash associated with epidermal growth factor positive cancers and tyrosine kinase inhibitors. It allowed continuation of the antineoplastic treatment (Alexandrescu et al. 2007).

Studies with combination products:

The efficacy and tolerability was evaluated of a new lotion containing menthol and colloidal oatmeal in patients with itch and cutaneous xerosis (n=54). Patients treated with Aveeno Skin Relief Moisturizing Lotion once daily for 3 weeks. After treatment, clinical examination, and the self-administered questionnaire revealed a significant improvement of cutaneous lesions including erythema, scaling, scratching lesions, lichenization, and pruritus in 52 of 54 treated patients (96%). Complete regression of cutaneous lesions and pruritus was achieved in 48 of 54 (88.9%) patients; whereas a partial remission was observed in 4/54 (7.4%) subjects and no improvement in 2/54 (3.7%) subjects (Pacifico et al. 2005).

The efficacy and safety was evaluated of A-Derma Exomega cream in a total of Japanese 55 patients with atopic dry skin. A-Derma Exomega cream is a cosmetic emollient containing Avena Rhealba® (Oat) total extract and evening primrose oil. After 4 weeks of topical application, skin dryness, scaling and pruritus were reported to be greatly improved in almost all cases, and the moisture content of the *stratum corneum* was said to be increased significantly. The results of this study concluded that the product was safe and efficient in clinical application for the dry skin of atopic dermatitis, improving patients' quality of life (Mizuno, 2005).

Randomized control trials

A number of studies have been conducted on various oat preparations. Some of the studies involved foodstuffs such as oats cereals and oat bran enriched muffins. These studies are included to illustrate current research on oat preparations

Effect on serum lipids

During an 11-week, randomized controlled trial, two groups of patients (Hispanic Americans) received a corn cereal (n=79) or an oats-containing (n=73) cereal preparation. The main body mass index of the participants varied between 28.4 and 30.2 (patients with a BMI $\geq$ 38 were excluded).
At the end of the treatment period, total cholesterol in the oats group was 197.3 ($\pm$ 25.0) mg% (initial value of 209.0 $\pm$ 29.7 mg%). In the corn group total cholesterol did not change. The difference between both groups was significant ($P < 0.0003$). The change was nearly entirely due to a lowering of the LDL cholesterol as HDL cholesterol was not influenced (Karmally et al. 2005).

Following a 2 week run-in phase, 34 premenopausal women (22-53 years) were randomly assigned either to a control group or to a treatment group, which received 2 oat bran-enriched muffins per day (corresponding to 28 g/day) of oat bran) during 4 weeks. Compared to the control group (n=16) a mean increase in plasma HDL-cholesterol of 11.2% was seen in women eating the oat bran supplement (n=18) ($P = 0.01$). The total cholesterol decreased by 7.0% ($P = 0.002$). Results were similar after adjustment for age, apo E genotype and weight change (Robitaille et al. 2005).

Caloric restriction, fat modification and oat bran supplementation were part of the nutritional regimen within a 4 week lifestyle health program for 235 patients with overweight and hypercholesterolemia. Patients were divided into 2 groups: one lifestyle group (n=136) and another with the same lifestyle but als 35-50g oats per day (n=99). Male overweight but normocholesterolic subjects were selected as controls (n=55). In the oat bran enriched food group the most significant decreases in total cholesterol were seen (- 67.7 $\pm$ 37.2 mg%; $p < 0.01$). This decrease was mainly due to the influence on the LDL-cholesterol (Berg et al. 2003).

The food matrix or the food processing, or both, could have adverse effects on the hypercholesterolemic properties of oat beta-glucan. This was the conclusion of a comparison between the outcomes of 2 studies with oat beta-glucan added to bread or to orange juice. LDL-cholesterol did not differ between a group (n=23) eating bread and cookies with wheat fiber during 4 weeks, as compared to a group eating bread and cookies with beta-glucan from oats (5 g/day). When the wheat fiber and beta-glucan were incorporated into orange juice, LDL-cholesterol was significantly lower in the beta-glucan group ($p < 0.001$ for a decrease of 6.7% $\pm$ 1.8%). The study was done in a parallel cross-over design, during one week with 25 patients (18-65 years; BMI < 30; total cholesterol < 8 mmol/L) (Kerckhoffs et al. 2003).

Effect on blood flow and blood pressure

Brachial artery reactivity scans (BARS) were used to test the effect of oatmeal (60g) against vitamin C and E. The effect of acute (single dose) as well chronic (6 weeks) treatment was evaluated. Subjects (16 males $\geq$ 35 years and 14 postmenopausal females) were treated in a randomized, placebo controlled, double-blind, cross-over design with a 2 weeks wash-out period. Before measurement patients were provoked by a high-fat meal (50g predominantly saturated). Oats increased flow mediated vasodilation measured as percent diameter change before and after treatment. This effect was only significant when acute and chronic effects were pooled (Katz et al. 2004). The same results were previously obtained when comparing whole grain oat with whole grain wheat cereal during one month (n=50; cross-over design) Katz et al. 2001).

Month-long, daily supplementation with oat cereal may prevent postprandial impairment of vascular reactivity in response to a high-fat meal (50g predominantly saturated). Hyperemic flow in a brachial artery reactivity study (BARS) in the group of patients taking oatmeal or alpha-tocopherol was maintained, whereas it was reduced

A diet containing soluble fibre-rich whole oats can significantly reduce the need for antihypertensive medication and improve blood pressure control. Men and women (n=88) being treated for hypertension with a mean baseline blood pressure below 160/100 were randomized to whole grain oats-based or wheat-based cereals. More participants in the oats group were able to stop or to reduce their antihypertensive medication: 77% versus 42%. The oats group experienced a 24.2 mg% total cholesterol reduction and a 15 mg% drop in plasma glucose versus controls (Pins et al. 2002).

A weight-loss diet containing oats was associated with favourable decreases in systolic blood pressure (oats - 6 $\pm$ 7 mmHg versus control – 1 $\pm$ 10 mmHg; $p = 0.026$) and blood lipids (oats – 0.87 + 0.47 mmol/L versus control – 0.34 + 0.5 mmol/L; $p < 0.003$) compared with a control diet without oats. This result came out of a study with 43 adults (BMI 26.4 $\pm$ 3.3) participating in an 8 weeks study. Weight reduction was comparable in both groups (oats – 3.9 $\pm$ 1.6 kg versus control -4.0 $\pm$ 1.1 kg) (Saltzman et al. 2001; 131: 1465-1470).

Cutaneous use

A cutaneous irritation double blind study with 12 volunteers was conducted by Vié et al. (2002). The participants were pretreated with 20 or 30% colloidal extracts in Petrolatume under occlusion during 2 hours. Control treatment consisted of Petrolatume. Sodium laurylsulfate was used as an irritant. Irritation was evaluated from the redness of the skin and cutaneous blood flow. Avena protected the skin from irritation as resulted from both parameters.

A comparison between 2 shower and baths oils was made during a 10 month period in 35 acute burns patients. The active product contained liquid paraffin with 5% colloidal oatmeal against the vehiculum (liquid paraffin). Patients were asked to rate their discomfort from itch and pain twice daily. Evaluation was made assessor-blinded. The group using the oatmeal preparation scored better than the vehiculum and required significantly less antihistamine medication (Matheson et al. 2001).

The corticoid sparing effect of a cutaneous oat extract was evaluated in children (n=173 under 12 years old) with atopic dermatitis during 6 weeks. Children were randomly assigned to the active preparation or to placebo. Utilisation of local corticoids, the Scoring Atopic Dermatits Index (SCORAD) and the quality of life of the infants (Infant's Dermatitis Quality of Life Index) and parents (Dermatitis Family Impact) were used as outcomes. There was a decrease of 42% of topical corticoid use in the intervention group ($P<0.05$) vs. 7.5% in the control group. The SCORAD index, and infants' and parents' quality of life significantly improved ($P<0.0001$) in both groups (Grimalt et al. 2007).

Assessor's comments
Clinical trials with oats preparations are of relatively recent origin. The possible therapeutic benefits of oats in case of hypercholesterolemia and cardiovascular complications cannot be considered as being within the traditional usage. The data available are not yet sufficient to support the efficacy of *Avena sativa* (fructus) in patients at cardiovascular risk; this aspect can be considered as an emerging science.
Although cutaneous use of *Avena sativa* has been studied in several open and controlled trials, a well established use cannot yet be accepted for several reasons. The patients included in clinical trials vary widely as far as their pathological condition is concerned. Children as well adults are studied. Inclusion of atopic patients, patients with iatrogenic rash due to the administration of several medicines, children who needed general skin care and patients with burns makes the evaluation of a well established indication difficult. The studies involved a range of different products with *Avena sativa* applied as an ointment or cream, oily liquid extract, colloidal oatmeal in liquid paraffin or as a lotion. The duration of treatment varied from 3 weeks to 10 months. Furthermore, the outcomes measured were quite variable: remission of skin lesions, level of satisfaction, skin dryness with physicochemical measuring of the moisture content of the skin, patient discomfort, Scoring Atopic Dermatitis Index (SCORAD) and quality of life. A well established use can only be accepted when the inclusion criteria (patients), the treatment (process) and the measured outcomes (product) are converging.

Use during pregnancy and lactation

No data available.

III.3. Traditional use

It is not known from what age *Avena sativa* has been used medicinally. Most probably the plant generated from Asia proxima. Cultivated oats are probably related to the species *Avena fatua*, originating from the Mediterranean Sea region. Oats were already cultivated 4000 years ago in Europe. Hippocrates, Plinius the Old and Galenus recommended oats for its tonic and feeding properties.

Hildegard von Bingen (12th century) describes the plant in her 'Physica': *... may everyone who is exhausted with an empty mind take steam bath by poring water wherein oats have been cooked over hot stone. If this treatment is repeated, the patient will get to himself again and regain the capacity of thinking ...* (http://plantaardigheden.nl/plant/beschr/gonnve/haver.htm)
Rembertus Dodoneus (1608) mentioned *Avena sativa* as a useful treatment against bowel disorders and as a diuretic.

The traditional use of *Avena sativa* extends over several therapeutic areas (Leclerc, 1947, List & Hörhammer 1972; Madaus G Lehrbuch der biologischen Heilmittel 1938; Anonymus, British herbal Pharmacopoea 1976; Schneider 1985, Schneider 1990).

Use as a sedative

The traditional use as a sedating agent is reported in a number of sources.

Madaus (1938)
... in der Amerikanischen Medizin findet eine Tinktur aus Hafer Verwendung als Nerventonikum bei Chorea, Epilepsie, Insomnie, nervöser Erschöpfung, Alkoholismus und während der Opiumentwöhnung. Allerdings wird die Wirksamkeit in letzterem Falle von sachverständigen Beobachtern sterk bezweifelt ...
... The tincture of oats is used as a nervous tonic in the American medicinal practice in case of chorea, epilepsy, insomnia, nervous exhaustion, alcoholism and opium detoxification. According to objective reviewers the efficacy for the latter applications is doubtful ...

List & Hörhammer (1972) mention the use of oats (seeds) mother tincture: *... In der Homöopathie bei Neurasthenie und als Sedativum ...*

The British Herbal Pharmacopoeia (1976) and Hänsel et al. (1992) ,recommends the liquid extract 1:1 in 25% alcohol and a tincture 1:5 in 45% alcohol.

- Action: antidepressive, thymoleptic.
- Indications: depression, melancholia, menopausal neurasthenia, general debility.
- Specific indication: depressive states.

Schneider (1985) recommends oats in case of nervous exhaustion, insomnia and nervous weakness. For these indications the mother tincture of the fresh flowering plant is used (HAB34).

Van Elteren (2007) recommends *Avena sativa* in case of nervous irritation, depression, sleeplessness, nervous exhaustion, nervous weakness, hysteria. The seeds as well as fresh oats are used.

Cutaneous use

External use is frequently mentioned in the concept document by Fabre (2004).
In the table below detailed information is given about traditional cutaneous use. References with* are cited from Fabre (2004). In general there is an substantial tradition in Europe, in particular in France and Germany, and the USA.

Table 4: Traditional cutaneous use of Oats preparations

Author (year)	Reported usage
* Planchon G. & Collin E. 1895	'Emollient' activity was mentioned in 'Les Drogues simples d'Origine Végétale'.
* Fournier P. 1947	Warm cataplasms of oats prepared with diluted acetic acid are used in case muscle spasms and lumbago. A pasta made with oat's flour mixed with beer yeast is used on infected ulcers and wounds, and to facilitate cicatrisation.
* Laude B. 1988	The author reviews the dermatological use of oats.
* Hyde JK. 1900	Oats can alleviate itching when used in baths.
* Leod Mac 1920	Itching in case of erythema is cured with a preparation made of oat's flour.
* Ormsby OS. 1921	The author used oat fruits to 'soften' the water in case of inflammatory dermatological conditions.
* Stockes JH. 1930	The author treated pruritus with oat mucilage.
* Andrews GC 1930	Oats alleviate dermatitis in patients suffering from acute chronic dermatological exfoliative affections.

* Spinka J. 1939	Oats is mentioned as an ingredient in baths and as a lotion, and as a cataplasm for treatment of burnings.
* Muscher M. 1948	Author of a brevet on a preparation made from comminuted fruits, resulting in a protein-polysaccharide complex.
Dick LA. 1958	Use of Avena as an emollient in pediatric dermatoses.
Franks AG. 1958	Dermatological use of Avena in baths.
Leone F. 1957 MonteBovi AJ. 1954	Use of Avena in the treatment of diaper rash.
Smith GC. 1958	The author makes an overview of colloidal demulcents with Avena amongst them. Avena mentioned in the treatment of various dermatoses.

There is a patent from 1944 (Anonymus, 1944) on a special oats fraction, relatively low in starch and relatively rich in protein. The preparation is intended as an ingredient for cosmetics including hand lotions, face creams, for baths or for application where a high viscosity and adhesiveness are desired.

Table 5: Use for other purposes

Nervous system
When alcoholic extracts of *Avena sativa* (fresh plant selected just before harvest: 1.5 parts of the plant were used on a group of opium addicts several patients reported a loss of interest in smoking. These positive results could not be repeated in another clinical study (Anand 1971; Bye et al. 1974).
Endocrinology
Should be useful in case of Premenstrual Syndrome (PMS) and depressions related to the menopausal status. Should also be an aphrodisiac for men as well as for women. Oats can also lower the blood sugar with a positive effect on diabetes: in this case the mucilage is used to lower the amount of glucose.
External use
Water preparations of *Avena sativa* can be applied as a gauze in case of all kind of dermatological problems like (wet) eczema, skin infections and psoriasis. Can also be applied in case of burns and itching. External use is further mentioned as warm cataplasm in case of lumbago. Oats preparations should relieve inflammations of the skin and should help cicatrisation.
Gastrointestinal tract
Avena sativa is used in case of diarrhea. It has a positive effect in liver function and stomach complaints. Regular use of oats optimizes defecation. The mucilage in case of gastro-enteritis and dyspepsia.
General condition
The mucilage is used to sustain recovery in case of a serious disease and loss of appetite occurs.
Respiratory tract
In case of cough, gauze impregnated with an oats preparation should be applied on the throat. It is used in case of respiratory infections.
Urinary tract
Since the 19th century Kneipp is a fervent promoter of the oats tea in case of rheumatic disease and gout. The tea is still recommended as a diuretic. Leclerc (1947) provided an exhaustive list of traditional applications of oats. They are among others related to urinary tract diseases.

IV. SAFETY

IV.1 Genotoxic and carcinogenic risk

No data available.

IV.1.1 Preclinical data

Mutagenicity and carcinogenicity

No data available.

IV.1.2. Clinical data

No data available.

IV.2. Toxicity

Acute toxicity

An avenathramide enriched mixture did not show any cytotoxicity to human aortic endothelial cells in concentrations up to 40 µg/ml (Liu et al. 2004).
Irritation tests using colloidal extracts of Avena sativa revealed no ocular or cutaneous toxicity. There was no sensitisation or photosensitisation seen. Concentrations of 2 to 100% were tested (Fabre 2004).

Subchronic and chronic toxicity

There are no data available on oral use.
Colloidal Avena extracts are incorporated in different cosmetic formulations such as shampoo, soap, creams, ointments, emulsions and gels. These products have been available commercially since 1982. These preparations are classified as well tolerated with cosmetovigilance index of < 0.2/10,000 units.

Reproductive toxicity

No data available

IV.3 Contraindications

The use of preparations containing Avena species is contraindicated for persons with a known hypersensitivity to this plant.

IV.4 Special warnings / precautions

Cutaneous tolerance

Varjonen (1995) warned against cutaneous use of Avena preparations in atopic children, after investigating the effects of these preparations in prick tests. Most probably the protein fraction (46 to 66 KD) was responsible.

Seven preparations were dermatologically tested in 114 patients suffering from atopic dermatitis and 115 patients with contact eczema: 3 preparations containing 3% of different total oats extracts in petrolatum ointments or glycerolic solutions, 3 preparations containing 0.5% of different oats protein fractions also in petrolatum ointments or glycerolic saline and pure petrolatum as a control. Evaluation was made after 48 and 96 hours. In both dermatological conditions the frequency of allergic reactions was reported as reduced. (El Bakali et al. 2000).

Similar results were obtained with a group of atopic children (n=202; age: from 1 month to 15 years). A patch test with total oats extract (3%) or protein fraction (0.5%) in petrolatum and prick test with the same concentrations in glycerolic saline. Five children gave a positive reaction (= 2.4%) (Rancé 2001).

Systemic tolerance

A double blind multicenter study was performed to test tolerability of oats in 116 children with newly diagnosed coeliac disease. During one year, one group received a standard gluten free diet, the other received wheat free oats (mean = 15g per day). Both groups did not differ significantly at the end of the study regarding coeliac serology markers or small bowel mucosal biopsies, including the numbers of intraepithelial lymphocytes (Högberg et al. 2004). Oats were well tolerated by coeliac patients (n=18). The median daily intake of oats was 93g/day (range 27-137 g) during 6 months to 2 years (Storsrud et al. 2003). However, another study reported more intestinal symptoms with oats (50g per day; n=23) than with a traditional gluten free diet (n=16) in coeliac disease patients. Patients taking oats suffered significantly more often from bowel complaints (diarrhoea and constipation). The villous structure did not differ between both groups, but the density of intraepithelial lymphocytes was slightly but significantly higher in the oats group. The levels of antibodies did not increase during the study period (Peraaho 2004). It should be noted that oats can be contaminated by wheat. Villous atrophy and dramatic dermatitis were reported in a coeliac patient after a first and second challenge with oats (Lundin et al. 2003). Up to 5 years of follow-up gave comparable results between a group eating a gluten free diet with or without oats (n=92; randomly assigned to one of the treatments). This study has been contested because of the limited number of patients completing the study (n=23 in the oats group versus n=28 in the control group) (Janatuinen et al. 2002; Dor & Shanahan, 2002). A survey concluded to safe use. Coeliac patients should be advised to consume only those products tested and found to be free from contamination (Thompson 2003).

IV.5 Undesirable effects

No data available.

IV.6 Interactions

No data available.

IV.7 Overdose

No data available.

V. OVERALL CONCLUSION

Avena sativa L. has been known for more than 4000 years as a food and the traditional medicinal usage of *Avena sativa* has been documented since the 12th century.

The dried fruits have been used traditionally for the relief of various skin conditions as cutaneous treatments, such as bath preparations, as colloidal extracts of oat flour mixed with a suitable vehicle or as oatmeal in liquid paraffin.

The oat herb, harvested before flowering, has also been used traditionally as an herbal sedative usually administered as a herbal tea, as aqueous or ethanolic extracts or as expressed juice from the fresh herb.

Recent studies with cutaneous preparations show some benefit in treating various skin conditions. However, further evidence is needed from properly designed trials to substantiate the therapeutic efficacy of the preparations tested.

Similarly, recent investigations into the potential therapeutic effects of oat preparations on patients with hypercholesterolemia and cardiovascular complications are of interest but further evidence of efficacy from properly designed clinical trials is needed to confirm the therapeutic effects.

The clinical data available do not support well established medicinal use of *Avena sativa* fruit or *Avena sativa* herb.

On the basis of the traditional evidence, sufficient data are available to develop Community herbal monographs for *Avena sativa* fruit and *Avena sativa* herb.

The following traditional uses are supported by the bibliographic data:

Table 6 Traditional uses for *Avena sativa* fruit and *Avena sativa* herb

Avena sativa fruit	Traditional herbal medicinal product for the symptomatic treatment of minor inflammations of the skin (such as sunburn) and as an aid in healing minor wounds.
Avena sativa herb	Traditional herbal medicinal product for the relief of mild symptoms of mental stress and to aid sleep.

Avena sativa fruit

There are no significant safety concerns with the use of the fruit preparations provided they are not used by individuals who are hypersensitive to *Avena* species. Skin reactions may occur in atopic patients and those with contact dermatitis.

Avena sativa herb

There are no significant safety concerns with the use of the herb preparations provided they are not used by individuals who are hypersensitive to *Avena* species. The usual precautions for herbal sedatives also apply to *Avena* herb. In addition, caution should be advised in coeliac patients as data on possible protein content are usually not available.

Genotoxicity data are not available for *Avena sativa* fruit and *Avena sativa* herb and thus entries to the Community list are not possible at this time.