PHYTOTHERAPY RESEARCH
Phytother. Res. (2009)
Published online in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/ptr.2751

An Extract from Wild Green Oat Improves Rat Behaviour

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An extract of wild green oat (*Avena sativa* L.), was tested *in vivo* in rats for its behavioural effects after chronic oral administration via extract-admixed food. Thirty six male Sprague-Dawley rats received (A) standard diet (controls), (B) 10 g/kg extract-admixed food or (C) 100 g/kg extract-admixed food. The following behavioural tests were performed: elevated plus maze, forced swimming, conditioned avoidance response and tetradic encounter. Body weight, food and fluid consumption were measured and apparent physical appearance was determined twice a week. Apart from a slightly decreased food and fluid intake in the high dose group there were no side effects observed during the treatment. The low dose led to an improvement of active stress response, an enhancement of shock avoidance learning and an increased synchrony in social behaviour. It may be concluded that the wild green oat extract is suitable to improve behavioural initiative in different situations. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords: wild green oat (*Avena sativa* L.); rat; anxiety; depression; social behaviour; stress.

INTRODUCTION

Extracts from green oat have been used traditionally to support mental health and cognitive function (Müller, 1990; Wichtl, 2002). In contrast to oat grain extracts, these extracts are produced from young oat plants. Central nervous system (CNS) indications for oat herb include anxiety, tension, stress, excitation and neurasthenia. However, the effectiveness of such preparations has not been documented so far (Klein and Blumenthal, 1998). The extract used in the present study was developed by a bioassay-guided approach where more than 30 accessions of *Avena sativa* L. were screened for their biological activity in various *in vitro* test systems. The accession chosen for extract manufacturing showed promising activity in a physiologically significant inhibition of the neurotransmitter metabolizing enzyme monoaminoxidase B (MAO-B) and of the cAMP degrading phosphodiesterase 4 (PDE-4) (Moccetti *et al.*, 2006; Wullschleger, 2006). These enzymes may play a modulatory role in anxiety, memory and depression (Houslay *et al.*, 2005; Riederer *et al.*, 2004).

The present study was designed as the first attempt to confirm that a green oat extract can affect traditional CNS indications in an *in vivo* system. Therefore, the extract from wild green oat (*Avena sativa* L.), was tested, after chronic oral administration, for the following behavioural effects in rats: elevated plus maze to measure phobic fear; forced swimming to screen for antidepressant efficacy; conditioned avoidance response as one-trial learning and to assess the behavioural response to an aversive situation; tetradic encounters to assess social behaviour.

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MATERIALS AND METHODS

Extract. The wild green oat extract was obtained from Frutarom Switzerland Ltd (Neuravena® (EFLA®955)). Dried above ground parts of the selected variety of *Avena sativa* L. were treated with aqueous ethanol (30% m/m), filtered according to a patented filtration process and spray-dried. 28% (m/m) Maltodextrinum Ph. Eur. was added as a carrier together with 2% (m/m) of silica colloidalis anhydrica Ph. Eur. The drug to extract ratio (DER) was 3.5:1. The extract was characterized by the flavonoid content (calculated as isovitexin). The batch used for the behavioural tests had a flavonoid content of 0.64% (m/m).

Animals and housing. Thirty six young male Sprague-Dawley rats were used, weighing 215 ± 10 g (mean ± SEM) at the beginning of the study. They were housed singly in Makrolon cages ($43 \times 26 \times 15$ cm^3) that were changed twice a week. Housing and testing took place in air-conditioned rooms controlled for temperature (21 ± 2 °C) and humidity (40–60%) under a 12:00/12:00 light/dark rhythm with lights on at 4:00 a.m. The animals received food and water *ad libitum* throughout the study. All experiments were performed in accordance with international ethical standards and the German Animal Protection Law (Approval ME 13/06).

Extract administration. The trial consisted of three experimental groups, further referred to as the control group, the low dose group and the high dose group. The low dose was chosen arbitrarily: a 1% admixture to rat diets seems a common, well-tolerated level of admixture in animal trials. Animals of the high dose group received a 10-fold higher extract dose than the animals of the low dose group. This broad spectrum

Received 4 January 2008
Revised 31 July 2008
Accepted 28 October 2008

was chosen to make sure that extract related effects in the different assays would show.

After 1 week of acclimatization, the extract was administered chronically, for 7 weeks, via extract-admixed food: the control group received standard diet (3430 KLIBA NAFAG standard mice/rat diet, Provimi Kliba AG, Switzerland); the low dose group received 10 g/kg extract-admixed diet; the high dose group received 100 g/kg extract-admixed diet.

Housing data. Body weight, food and fluid consumption were measured twice a week and individual time courses of body weight, food and fluid intake, and extract doses (g/kg body weight (BW)/day) were calculated.

Home cage observations and pathology. Twice a week, home-cage-observations were performed that comprised a rating of physical appearance, reaction to handling, occurrence of diarrhoea and any other remarkable behaviour. On completion of the behavioural tests, three animals of each group were killed and sent to the CVUA (Stuttgart, Germany) for macroscopic analysis of liver, spleen, kidney, heart, lungs, stomach and intestine.

Elevated plus maze (EPM). The elevated plus maze test (Pellow and File, 1986) is used to measure phobic fear as well as exploration and locomotor activity.

The EPM consisted of two black wooden open arms (50×12 cm^2) and two closed arms ($50 \times 12 \times 40$ cm^3). The apparatus was elevated to a height of 50 cm above the ground. Testing was performed in week 6 of the study, during the dark phase. The animal was placed in the centre of the maze facing an open arm and was left there for 5 min. If the animal fell down from the maze, it was replaced into the centre. Behaviour was registered by video. The video signal was transferred by frame-grabbing and object-tracking software into a time series of the *x*- and *y*-coordinates of the animal. Time series analysis comprised the time spent and the distance travelled in open and closed arms, the total distance travelled as well as latency to enter the terminal area of an open arm.

Forced swimming (FS). The forced swim test is a tool to screen for antidepressant activity (Porsolt *et al.*, 2000).

The apparatus consisted of a transparent Plexiglas cylinder (20 cm in diameter; 50 cm high). It contained water (20–22 °C) to a height of 20 cm. The training session and the testing were performed in week 8 of the study, during the light phase. The animal was placed into the water and left there for 15 min (1st trial) or 5 min (2nd trial, 24 h after the 1st trial). Behaviour was recorded by video and rated by an experienced ethologist (inter-rater reliability given by Spearman correlation: sr = +0.91) using the following behaviours: floating (no activity) and struggling (active movements to keep the head above water).

Conditioned avoidance response (CAR). The conditioned avoidance response test can be used as a one-trail learning paradigm (Bauer, 1978); it may also be used to assess the behavioural response to an unknown aversive situation.

The CAR apparatus consisted of a Plexiglas built shuttle-box with two compartments (26×26 cm^2), divided by a wall of full height. The animal can shuttle between the two compartments through a hole in the wall (8 cm in diameter, 2 cm above the ground). A precision regulated shocker (Coulborn, USA) administering foot shocks (0.1 mA) over a metal grid in the box floor served as an unconditioned stimulus (US). For conditioned stimuli (CS), a buzzer (0.5 Watt) and two light bulbs (2.2 Watt) were used, mounted to the lid of the box. The apparatus was placed within infrared monitoring frames (40 beams in *x* and *y* direction, each) enabling an automated conduction of the experiment based on the registration of the animal's location. Testing was performed in week 7 of the study, during the light phase. The rat was placed in the shuttle box for 30 min. A trial consisted of 60 runs of 30 s each. During each run, the CS was presented after 20 s for 5 s. If the animal changed the compartment before the onset of the US, the CS was turned off and no further action took place for the remaining time of the run. If the animal failed to change the compartment within the 5 s of CS presentation, the US was turned on (CS still on). The US stayed on until either the animal changed the compartment or a timeout of 5 s occurred. In either case, the next run began. The animal's response was registered in a data file as avoidance (rat shuttles prior to shock), escape (rat shuttles during shock) or failure (rat does not shuttle) (Arnt, 1982).

Tetradic encounter (TE). To assess social behaviour, a tetradic encounter test was performed (Wolffgramm, 1990). Beside analysis of the number and duration of different social behaviours, it enables more complex interactions between animals to be analysed, such as social appetence/withdrawal and adequate/inadequate social behaviour.

The training sessions and the testing were performed in weeks 4 and 5 of the study respectively, during the dark phase. Four animals of the same experimental group were placed together in a black-painted open field (1×1 m^2) for 15 min. The animals were individually marked by black symbols on their back. The rats were familiarized with the situation by three training sessions in the same arrangement. Behaviour was recorded on video. From these tapes, an experienced ethologist evaluated the trajectory of each rat and rated the behaviour according to non-agonistic social activity, aggressive acts, defensive acts and non-social activity. A Spearman's rank correlation coefficient of sr = +0.95 for the accuracy of rating and a cross-coincidence coefficient cc = +0.67 indicating temporal accuracy proved a sufficiently high reliability of rating. The two time series of each animal were analysed according to the number and time spent with behavioural patterns; spatial behaviour (stays in corners and centre, use of space), distance between animals and interindividual behavioural synchrony. The latter was assessed by means of cross-correlations between pairs of rats (each rat versus each encounter mate) on the basis of Spearman's rank correlation coefficients (Wolffgramm and Heyne, 1990).

Reference compounds. As this study was intended to screen for behavioural effects of the extract, reference compounds were not included. To assess validity and reliability, the results of the present study will be compared with those deriving from medimod's database (identical protocols as in the present study):

DOI: 10.1002/ptr

EPM: Chlordiazepoxide 3 mg/kg i.p.
FS: Imipramine 3 × 15 mg/kg i.p. (Porsolt *et al.*, 2000)
TE: As changes in social behaviour are indicative for several CNS diseases, no specific reference compounds exist.
CAR: No clinically effective reference compound available.

Statistics. Statistics were performed using a general linear model (GLM) with dose as single factor; data of the control group were treated as 0-dose. Time series were analysed using a bifactorial GLM with dose as the first and time as the second factor. To analyse group differences, at a given time point of a time series, global statistics were performed using non-parametric Kruskall-Wallis H-test. If a statistically significant difference occurred, data were further analysed by Mann-Whitney U post-hoc tests. In all cases, a result of $p < 0.05$ (two-tailed testing) was considered significant.

RESULTS

The high dose of the extract attenuated body weight gain and food intake, and generally increased fluid intake (Table 1). The low dose reduced food intake at the end of the experimental period. During the first week, the mean dose was 0.98 g/kg BW/day and 9.28 g/kg BW/day, respectively. In both groups, the doses decreased with time because the food intake did not increase at the same rate as the body weights did. Home-cage observations revealed only minor, short-lasting and non-significant deviations from normal (data not shown). Macroscopic analysis of the inner organs revealed no pathological results.

In all four behavioural tests, the results of the control group were according to the results obtained in earlier experiments collected in the laboratory's database.

The extract revealed no significant effects in EPM, either on anxiety (time spent in open arms) or on exploration or locomotion (distance travelled) (Table 2).

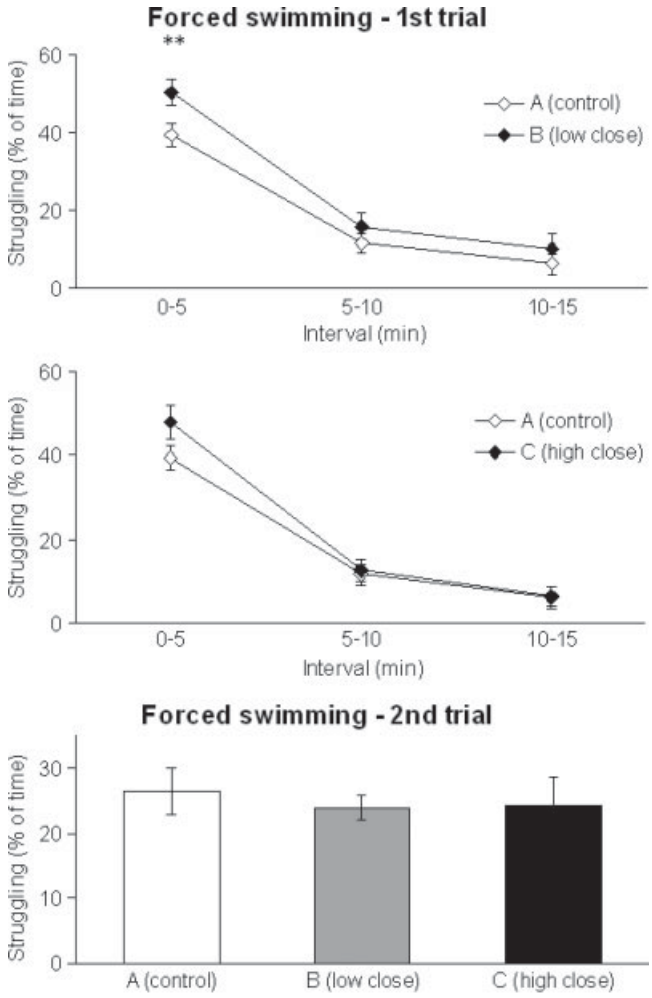
Table 1. Mean (± SEM) body weight, food intake, fluid intake and extract dose in weekly intervals over course of the experiment. GLM-statistics for each parameter are presented in the lower section. Test groups: A (control): Standard diet; B (low): 10 g/kg extract, C (high): 100 g/kg extract

	Body weight (g)			Food intake (g/day)			Fluid intake (mL/day)			Extract dose (g/kg BW/day)	
Week	A (control)	B (low)	C (high)	A (control)	B (low)	C (high)	A (control)	B (low)	C (high)	B (low)	C (high)
0	230.17 (2.23)	232.67 (1.25)	234.42 (1.75)	25.38 (0.39)	25.15 (0.33)	25.75 (0.33)	29.14 (0.94)	27.73 (0.64)	28.97 (1.15)		
1	300.25 (2.92)	307.13 (1.89)	301.25 (2.49)	30.50 (0.57)	30.10 (0.28)	27.81 (0.51)	33.07 (1.04)	33.91 (1.03)	43.41 (1.73)	0.98 (0.01)	9.23 (0.14)
2	358.58 (4.16)	367.17 (2.31)	352.83 (4.13)	31.33 (0.53)	31.11 (0.30)	30.42 (0.57)	35.10 (1.23)	34.33 (0.77)	45.30 (1.85)	0.85 (0.01)	8.61 (0.09)
3	404.25 (5.59)	411.88 (3.20)	395.17 (5.98)	32.17 (0.71)	31.72 (0.51)	31.23 (0.66)	34.10 (0.85)	32.85 (0.65)	43.77 (1.78)	0.77 (0.01)	7.90 (0.10)
4	442.92 (6.98)	448.00 (4.92)	430.42 (7.13)	31.68 (0.71)	30.95 (0.57)	30.67 (0.41)	34.74 (1.13)	33.45 (0.65)	44.92 (2.50)	0.69 (0.01)	7.14 (0.11)
5	476.54 (8.07)	479.21 (6.44)	461.83 (7.81)	31.70 (0.81)	30.49 (0.55)	30.32 (0.50)	34.76 (1.13)	33.04 (1.31)	42.64 (1.93)	0.64 (0.07)	6.57 (0.07)
6	501.17 (9.14)	503.04 (7.53)	483.63 (8.44)	31.52 (0.78)	29.90 (0.55)	29.12 (0.46)	36.71 (1.63)	33.69 (1.17)	41.57 (2.04)	0.59 (0.01)	6.03 (0.07)
7	520.42 (10.19)	522.83 (8.31)	500.33 (9.01)	30.76 (0.68)	29.21 (0.44)	28.86 (0.52)	37.11 (1.49)	33.98 (1.18)	43.29 (2.63)	0.56 (0.004)	5.77 (0.07)
Statistics	Group: F(1,33) = 1.85; $p = 0.17$ Time: F(15,495) = 2558.45; $p < 0.001$ Group × time: F(30,495) = 2.09; $p < 0.001$			Group: F(1,33) = 2.10; $p = 0.14$ Time: F(15,495) = 116.29; $p < 0.01$ Group × time: F(30,495) = 4.07; $p < 0.01$			Group: F(1,33) = 13.36; $p < 0.001$ Time: F(15,495) = 38.10; $p < 0.001$ Group × time: F(30,495) = 5.69; $p < 0.001$				

Table 2. Behaviour in EPM (mean ± SEM and GLM-statistics for each parameter). Test groups: A (control): Standard diet; B (low): 10 g/kg extract, C (high): 100 g/kg extract

	Mean (± SEM)			Statistics	
	A (control)	B (low)	C (high)	F(2,33)	p
Time in open arms (%)	24.70 (2.30)	26.00 (3.00)	28.20 (4.10)	0.30	0.74
Time in closed arms (%)	45.00 (2.00)	41.50 (2.10)	36.80 (3.50)	2.47	0.10
Total distance travelled (cm)	1514.40 (55.50)	1477.20 (33.70)	1384.10 (70.50)	1.47	0.24
Latency to enter open arm (s)	29.60 (17.80)	10.40 (3.30)	26.40 (8.60)	0.79	0.46

DOI: 10.1002/ptr



In the training session of FS, the low dose significantly enhanced struggling in the first 5 min of the session (Fig. 1). In the test trial, no group differences were found.

To assess CAR learning, a performance score was calculated (2, avoidance; 1, escape; 0, failure). Animals of the low dose group had a significantly higher score than both controls and the high dose group (Fig. 2). In a second step, the three responses were regarded separately. In the low dose group, the number of failures was significantly lower compared with both control and high dose group (Fig. 2). Analysis of the time course of learning revealed that animals of this group learned faster (Fig. 2).

The extract had no effects on locomotor activity, spatial preferences, behavioural patterns or distance to partners (Fig. 3, Table 3). However, interindividual behavioural synchrony was higher and lasted longer in the extract-treated rats. When social patterns were analysed separately, the low dose group showed higher synchrony for non-agonistic ('friendly') social behaviour, whereas in the high dose group synchrony in aggressive behaviour (mutual agonistic interactions) was increased.

Figure 1. Time spent struggling in forced swimming. Top: time courses of control vs low dose group. Middle: time courses of control vs high dose group. Bottom: time spent with struggling during the second trial (5 min). Data are presented as mean ± SEM. Asterisks indicate significant differences in post-hoc U-statistics for a single time interval, ** $p < 0.01$. GLM-statistics for the second trial are given in the figure. Test groups: A (control), Standard diet; B (low), extract 10 g/kg; C (high), extract 100 g/kg.

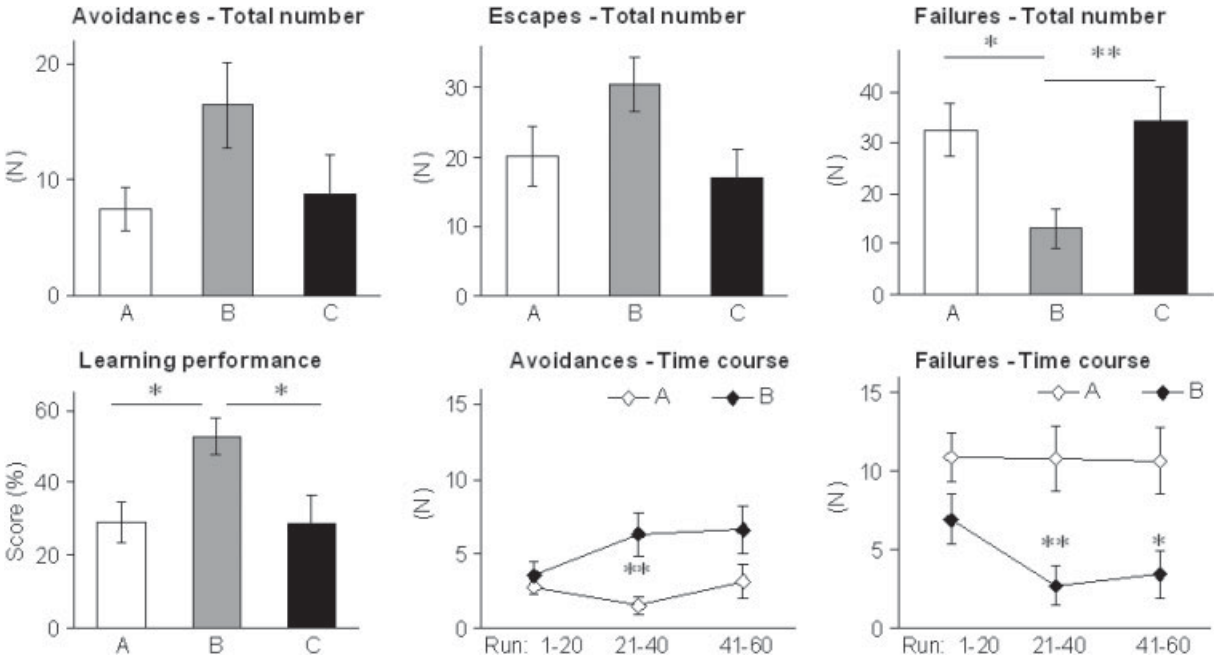


Figure 2. Conditioned avoidance response. Top: Number of avoidances, escapes and failures (mean ± SEM). GLM-statistics (avoidances/escapes/failures): F(2,32) = 2.59/2.93/5.06, $p = 0.09/0.07/< 0.05$. Asterisks indicate significant post-hoc statistics: * $p < 0.05$, ** $p < 0.01$. Bottom: left figure: learning performance (mean ± SEM). GLM-statistics: F(2,32) = 4.89, $p < 0.05$. Asterisks indicate significant post-hoc statistics: * $p < 0.05$. Middle and right figures: time course of avoidances and failures for the control vs the low dose group (mean ± SEM). GLM-statistics (avoidances/failures): Run: F(2,64) = 5.75/4.18, $p < 0.01/p < 0.05$; Group: F(2,32) = 2.59/5.06; $p = 0.09/p < 0.05$; Run × Group: F(6,64) = 2.01/1.86; $p = 0.10/p = 0.13$. Asterisks indicate significant U-test comparisons: * $p < 0.05$, ** $p < 0.01$. Test groups: A (control), Standard diet; B (low), 10 g/kg extract; C (high), 100 g/kg extract.

DOI: 10.1002/ptr

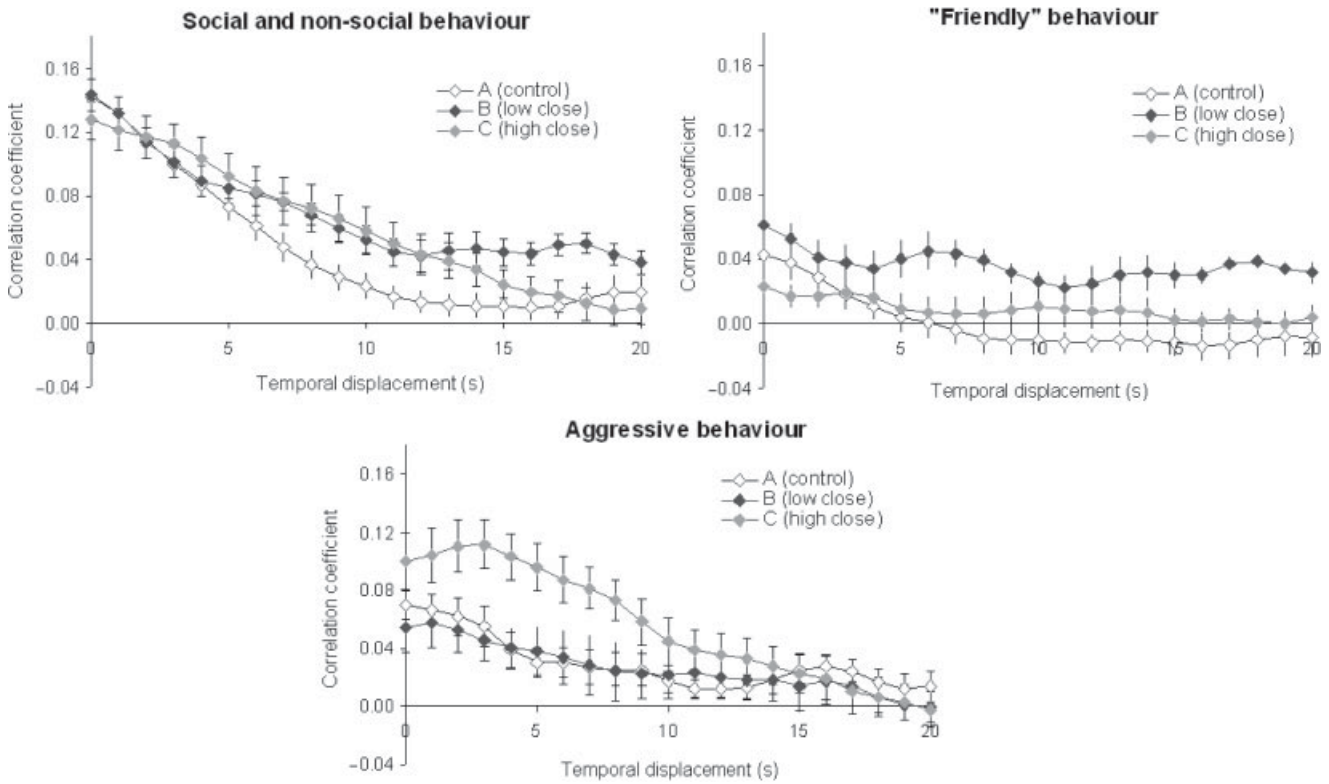


Figure 3. Interindividual behavioural synchrony in tetradic encounter (mean ± SEM). Upper figure left: Synchrony in both social and non-social behaviour for controls vs low and high dose group. GLM-statistics: Displacement: $F(20, 660) = 100.11$, $p < 0.001$; Group: $F(2,33) = 1.97$, $p = 0.16$, Group × Displacement: $F(40,660) = 2.91$, $p < 0.001$. Upper figure right: Synchrony in 'friendly' social behaviour for controls vs low and high dose group. GLM-statistics for all groups: Displacement: $F(2,660) = 7.43$, $p < 0.001$; Group: $F(2,33) = 7.52$, $p < 0.01$; Group × Displacement: $F(40,669) = 1.42$, $p < 0.05$. Lower figure: Synchrony in aggressive behaviour for controls vs low and high dose group. GLM-statistics for all groups: Displacement: $F(20,660) = 25.53$, $p < 0.001$; Group: $F(2,33) = 2.43$, $p = 0.1$; Group × Displacement: $F(40,660) = 3.52$, $p < 0.001$. Test groups: A (control), Standard diet; B (low), 10 g/kg extract; C (high), 100 g/kg extract.

Table 3. Behaviour in TE (mean ± SEM and GLM-statistics for each parameter). Test groups: A (control): Standard diet; B (low): 10 g/kg extract, C (high): 100 g/kg extract

	Mean (± SEM)			Statistics	
	A (control)	B (low)	C (high)	F(2,33)	*p*
Time spent with non-social behaviour (%)	64.2 (2.1)	66.4 (1.7)	65.7 (2.0)	0.33	0.72
Time spent with aggressive behaviour (%)	4.2 (0.9)	4.3 (1.1)	6.1 (1.0)	1.10	0.34
Time spent with non-agonistic social behaviour (%)	22.8 (2.1)	20.7 (1.6)	19.3 (2.1)	0.80	0.46
Time spent with defensive behaviour (cm)	8.9 (0.9)	8.6 (1.0)	8.9 (0.9)	0.03	0.97
Total distance travelled (m)	146.5 (8.4)	143.0 (6.8)	141.8 (5.6)	0.12	0.89
Time spent in the centre (%)	13.6 (1.1)	10.4 (0.7)	11.5 (0.9)	2.95	0.07
Mean distance to test mate (cm)	36.7 (0.8)	38.6 (0.4)	37.1 (0.7)	2.40	0.11

DISCUSSION

Data on physiological parameters, behavioural observations and macroscopic analysis of selected inner organs revealed no adverse effects of the extract. However, the high dose moderately affected food and fluid intake. Such side effects may point towards an inadequate dose, resulting in less relevant findings for the high dose group.

The more profound behavioural effects were observed in the CAR-test (learning/stress coping) and the TE-test (social behaviour).

The low dose was effective in accelerating memory formation compared with controls. This conclusion can be drawn from the CAR-test from the highly significant enhancement of avoidances in the middle sector of a learning trial; the controls learned the task not before the final sector. The low dose enhanced learning speed and reduced failures. Whereas avoidances

DOI: 10.1002/ptr

are a clear indicator for learning, the number of failures may be related to coping strategies (e.g. freezing (Driscoll, 1986)). CAR consists of a novel and aversive stimulus. Thus, the CAR results may be related to active or passive response to stressors, too. It is not yet clear whether improvement in avoidance learning is due to an enhancement of the active stress response that, in consequence, facilitates learning, or is a separate cognitive effect.

Disturbances of social behaviour are indicative for several mental diseases (e.g. Sams-Dodd, 1996). In the present study, the analysis of social behaviour was performed at different levels. The basic behavioural structure (time budget and spatial behaviour) was not affected by the extract. However, it does not reflect adequacy of social behaviour (e.g. friendly social approaches are responded by aggression). Adequacy was assessed by interindividual behavioural synchrony. Both doses caused an enhanced and prolonged synchrony in social behaviour. An enhancement of behavioural synchrony can be interpreted as increased social interest of the extract-treated animals and an improvement of the reactions to social signals from conspecifics.

The extract revealed no effects on phobic fear as measured in the EPM. The results from other trials with the same settings confirmed the reliability and validity of the data (e.g. time in open arms (%): controls: 19.2 ± 3.4; reference compound chlordiazepoxide: 37.0 ± 3.4). This finding is confirmed by the results from TE since animals did not differ in spatial parameters related to anxiety.

In the present study, the FS test showed only effects in the training session for the low dose group. The training session is commonly neglected in the interpretation. However, because it consists of a novel and aversive situation for the animal, it may even be highly interesting. In the training session, animals of the low dose group struggled more and floated less than the controls. This may be interpreted as an active coping strategy. Reduced coping abilities are characteristic of depressive states in both humans (Ruedi-Bettschen *et al.*, 2004) and rats (Takaoka *et al.*, 1988). The extract may therefore have mood-enhancing effects and support active rather than passive response to a stressor.

The extract did not enhance struggling in the FS trial, which is usually regarded as predictor for antidepressant efficacy (Porsolt *et al.*, 2000).

Although the validity of FS has been argued before (De Pablo *et al.*, 1989; Nomura *et al.*, 1982), results from other trials with the same settings confirmed the reliability and validity of the present FS data (e.g. time struggling (%): controls, 32.8 ± 3.9; reference compound imipramine, 62.6 ± 4.7).

The findings from the present study seem to be in good accordance with the *in vitro* inhibitory effects of the extract. MAO-B inhibitors are used for the treatment of Parkinson's disease (Riederer *et al.*, 2004) and non-selective MAO inhibitors are used for the treatment of depression (Quitkin *et al.*, 1990), anxiety and panic disorders (Heimberg *et al.*, 1998; Lydiard and Ballanger, 1987). Studies performed on the effects of MAO inhibitors in the EPM required acute administration (Johnston and File, 1988; Paslawski *et al.*, 1996). This may explain the negative EPM results in the present study. PDE 4 inhibitors are found to improve learning (Blokland *et al.*, 2006; Imanishi *et al.*, 1997). Studies performed on the effects of PDE 4 inhibitors in the FS showed increased struggling in the second trial (Zhang *et al.*, 2005), whereas escapes in CAR are reduced (Zhang *et al.*, 2005). Both effects are discussed as antidepressant efficacy.

In conclusion, the low dose increased active coping to a stressor, enhanced avoidance learning and improved synchrony in social behaviour. The extract is therefore suitable for improving behaviour in different test conditions.

Acknowledgements

We wish to thank the team of medimod for gently taking care of the animals and excellent performance of the behavioural tests.

This work has been conducted by medimod pharmacology services GmbH with the financial support of Frutarom Switzerland Ltd. medimod GmbH is an independent research organization, Frutarom Switzerland Ltd is in no way legally related to medimod GmbH. medimod GmbH itself has no financial interest in the results of the study and thus there has been no bias.

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DOI: 10.1002/ptr