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(71) Applicant: BOHNE ASKØY AS [NO/NO]; Romledalen 51, 5310 Hauglandshella (NO).

(72) Inventors: BOHNE, Øyvind; Romledalen 51, 5310 Hauglandshella (NO). BOHNE, Victoria; Romledalen 51, 5310 Hauglandshella (NO).

(74) Agent: ACAPO AS; P.O. Box 1880 Nordnes, 5817 Bergen (NO).

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(54) Title: PREVENTION AND/OR TREATMENT OF HYPERLACTATAEMIA

(57) Abstract: A nutritional or pharmaceutical composition for the prevention and/or treatment of hyperlactataemia or lactic acidosis is described. Also described is a pharmaceutical or nutritional composition for reducing the amount of lactate in the blood of an animal.



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Title: Prevention and/or treatment of hyperlactataemia

Field of invention

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The present invention relates to a composition for the prevention and/or treatment of hyperlactataemia or lactic acidosis, and a pharmaceutical or nutritional composition for reducing the amount of lactate in the blood of an animal.

10 Background of the invention

Hyperlactatemia is a medical condition where the level of lactate in the blood is above normal. Lactic acidosis is a medical condition characterized by the buildup of lactate (especially L-lactate) in the body, which results in an excessively low pH in the bloodstream. It is a form of metabolic acidosis, in which excessive acid accumulates due to a problem with the body's metabolism of lactic acid. Lactic acidosis is typically the result of an underlying acute or chronic medical condition, medication, or poisoning.

The inventors of the present invention have surprisingly found that oxalate or oxalic acid or derivatives or salts thereof have a curative effect on hyperlactataemia and lactic acidosis. We do not know the exact mechanisms of the active compounds but key metabolic pathways are modulated by the addition of the compounds of the present invention.

A number of voluntary persons, with and without hyperlactataemia and lactic acidosis have been tested, and the compounds of the present invention show a remarkable improvement of many biological parameters and symptoms.

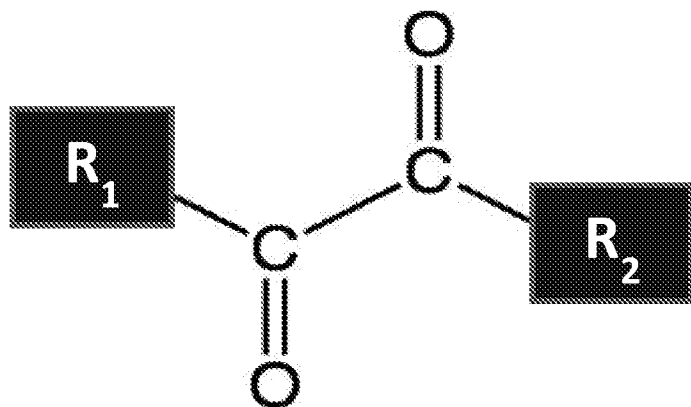
The inventors have also shown that the composition of the invention has a universal effect on lowering the level of lactate in the blood of a healthy person, and the composition can thus be used to prevent or treat diseases or symptoms related to a high level of lactate.

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Summary of the invention

A first aspect of the present invention relates to a composition for the prevention and/or treatment of hyperlactataemia or lactic acidosis, wherein said composition comprises oxalate or oxalic acid, or a salt, prodrug, derivative or metabolite thereof.

An embodiment of the composition comprises an oxalic compound of the formula



where;

$R_1=OH$ and $R_2=OH$ is oxalic acid, or

$R_1=H_2N$ and $R_2=ONa$ is sodium oxamate, or

$R_1=H_2N$ and $R_2=OK$ is potassium oxamate, or

$R_1=H_2N$ and $R_2=CaO$ is calcium oxamate, or

$R_1=O^-$ or $R_2=OH$ is hydrogenoxalate, or

$R_1=K^+O^-$, $R_2=OH$ is potassium hydrogenoxalate, or

$R_1=O^-$ and $R_2=O^-$ is oxalate, or

$R_1=NaO$ and $R_2=NaO$ is sodium oxalate, or

$R_1=CaO$ and $R_2=CaO$ is calcium oxalate

An embodiment of the composition comprises a compound selected from the group consisting of magnesium oxalate, potassium oxalate, oxalic acid anhydrous, oxalic acid dihydrate, lithium oxalate, cesium oxalate, oxaloacetic acid, lithium oxamate, cesium oxamate, magnesium oxamate, caesium oxalate, beryllium oxalate, potassium oxalate, oxalic acid anhydrous, oxalix acid dyhydrate, lithium oxalate, sodium oxalate, thallium (I) oxalate, uranyl oxalate, gallium oxalate, gold oxalate, magnesium oxalate, mercury (II) oxalate, manganese oxalate, nickel oxalate, barium oxalate, silver oxalate, iron (II) ferrous oxalate, scandium oxalate, cadmium oxalate, and calcium oxalate.

In an embodiment comprises the composition also lipoic acid, preferably alpha-lipoic acid (ALA).

In an embodiment comprises the composition thiamine, B₁. In an embodiment comprises the composition niacin, B₃. In an embodiment comprises the composition Riboflavin, B₂.

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In an embodiment comprises the composition a sugar. In an embodiment is the sugar one or more sugars selected from the group consisting of sucrose, glucose, fructose, maltose and lactose.

In an embodiment is the composition for the prevention and/or treatment of hyperlactataemia.

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In an embodiment is the composition for the prevention and/or treatment of lactic acidosis.

In an embodiment is the composition for use in the prevention and/or treatment of chronic fatigue syndrome (CFS)/ myalgia encephalomyelitis (ME)/ systemic exertion intolerance disease (SEID) or fibromyalgia wherein hyperlactataemia is a component or symptom.

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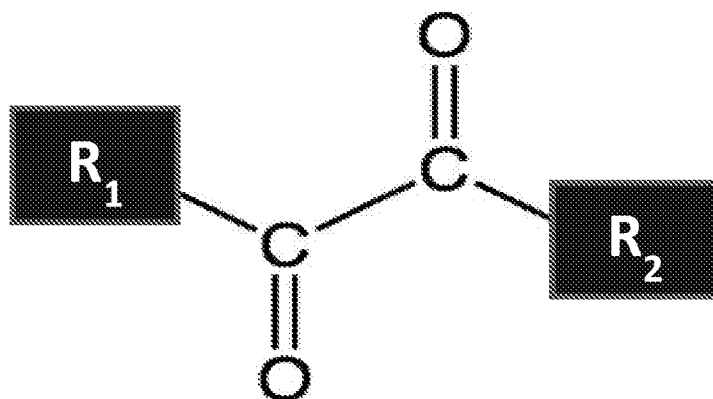
The hyperlactataemia can be with lactic acidosis, or it can be without lactic acidosis.

A second aspect of the present invention relates to a pharmaceutical or nutritional composition for reducing the amount of lactate in the blood of an animal, comprising administering said composition to a patient in need thereof, and wherein said composition comprises oxalate or oxalic acid, or a salt, prodrug, derivative or metabolite thereof.

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In an embodiment comprises said composition an oxalic compound of the formula

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where;

$R_1=OH$ and $R_2=OH$ is oxalic acid, or

$R_1=H_2N$ and $R_2=ONa$ is sodium oxamate, or

$R_1=H_2N$ and $R_2=OK$ is potassium oxamate, or

5 $R_1=H_2N$ and $R_2=CaO$ is calcium oxamate, or

$R_1=O^-$ or $R_2=OH$ is hydrogenoxalate, or

$R_1=K^+O^-$, $R_2=OH$ is potassium hydrogenoxalate, or

$R_1=O^-$ and $R_2=O^-$ is oxalate, or

$R_1=NaO$ and $R_2=NaO$ is sodium oxalate, or

10 $R_1=CaO$ and $R_2=CaO$ is calcium oxalate

In an embodiment comprises the composition a compound selected from the group consisting of magnesium oxalate, potassium oxalate, oxalic acid anhydrous, oxalic acid dihydrate, lithium oxalate, cesium oxalate, oxaloacetic acid, lithium oxamate, cesium oxamate, and magnesium oxamate.

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In an embodiment comprises the composition lipoic acid, preferably alpha-lipoic acid (ALA).

In an embodiment comprises the composition thiamine, B_1 . In an embodiment comprises the composition niacin, B_3 . In an embodiment comprises the composition Riboflavin, B_2 .

20

In an embodiment comprises the composition a sugar. Preferably, the sugar is one or more sugars selected from the group consisting of sucrose, glucose, fructose, maltose and lactose.

In an embodiment is the composition for the prevention and/or treatment of hyperlactataemia.

25

In an embodiment is the composition for the prevention and/or treatment of lactic acidosis.

In an embodiment is the composition for use in the prevention and/or treatment of chronic fatigue syndrome (CFS)/ myalgia encephalomyelitis (ME)/ systemic exertion intolerance disease (SEID) or fibromyalgia wherein hyperlactataemia is a component or symptom.

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In an embodiment is the Total Lactate Load or the amount of lactate in the blood reduced in an animal having a higher amount of lactate than normal.

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In an embodiment is the higher amount of lactate a consequence of physical training or exercise.

In an embodiment is the higher amount of lactate a consequence of intake of alcohol.

In an embodiment is the higher amount of lactate an effect of a disease.

5

In an embodiment is the reduction of lactate is for treatment or prevention of conditions selected from the group consisting of Biotinidase deficiency, multiple carboxylase deficiency, or nongenetic deficiencies of biotin; Diabetes mellitus and deafness; Fructose 1,6-bisphosphatase deficiency;

10 Glucose-6-phosphatase deficiency; GRACILE syndrome; Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; Pyruvate dehydrogenase deficiency; Pyruvate carboxylase deficiency; Impaired delivery of oxygen to cells in the tissues (e.g., from impaired blood flow – hypoperfusion); Bleeding; Polymyositis; Ethanol toxicity; Sepsis; Shock; Advanced liver disease;

15 Diabetic ketoacidosis; Excessive exercise (overtraining); Regional hypoperfusion (e.g., bowel ischemia or marked cellulitis); Cancers such as Non-Hodgkin's and Burkitt lymphomas and Pheochromocytoma or for use of medicaments selected from the group consisting of Linezolid; Phenformin; Metformin; Isoniazid toxicity; Propofol; Propylene glycol (D-lactic acidosis); Nucleoside reverse transcriptase inhibitors; Abacavir/dolutegravir/lamivudine; Emtricitabine/tenofovir; Potassium cyanide (cyanide poisoning); and Fialuridine.

20 Experimental section

The experiments conducted and the results obtained will be described in the examples below with reference to the figures;

25 Figure 1 shows a HPLC chromatogram of Freshly made Active drinkable (above) and freshly Quenched drinkable (below).

Figure 2 shows overlaid chromatograms of freshly quenched drinkable and Acid mix.

30 Figure 3 is a photo of spontaneous formed precipitate under the storage at 4-7°C in HPP-treated active drinkable.

Figure 4 shows a Lactatogram of participant 2 in example 2 (moderate exercising on weekly basis, taken one dose of 250 ml 50 minutes prior the test) during treadmill test: in truncated– quenched

drinkable; in blue squares – active drinkable; in green triangles – normal upper boarder line of 2.0 mmol/L.

Figure 5 shows the therapeutic effect in form of reduced Total Lactate Load measured as % reduced AUC at given time after intake of single 250 ml dose of oxalate mix in Active drinkable compared to Active drinkable with excess of CaCO_3 .

Figure 6 shows the Lactatogram of participant 20 (none exercising on weekly basis, taken one dose of 250 ml 50 minutes prior the test) during treadmill test: in truncated– quenched drinkable; in blue squares – active drinkable; in green triangles – normal upper boarder line of 2.0 mmol/L.

Figure 7 shows the therapeutic effect in form of reduced Total Lactate Load measured as % reduced AUC at given time after intake of single 250 ml dose of oxalate mix in Active drinkable with excess of CaCO_3 compared to Active drinkable.

Figure 8 shows increase of Lactate in capillary blood in response to single 250 ml dose of 13.5 % red wine in left foot (hallux, brown squares) and left hand (fingertips, blue circles) in male volunteer, 49 years old. The normal range shown in trunked black lines (Test 1).

Figure 9 shows increase in Lactate in capillary blood in response to multiple doses of total 500 ml red wine (13,5%) in male volunteer, 49 years old: left foot (hallux, in red squares) and left hand (fingertips in blue circles). Normal range in black trunked lines (Test 2).

Figure 10 shows lactate in capillary blood of left foot (hallux) during whole test (black circles) in male volunteer, 49-year-old and upper normal value (green squares) before, under and after consumption of 750 ml 13% red wine and 100 ml 40 % whisky (test 3).

Figure 11 shows Lactatogram for 155 min for male volunteer, 49 years old. The lactatogram had been taken in context of the reading test (functional diagnostics of ME/CFS/SEID/Chronic Hyperlactatemia).

Figure 12 shows lactate in left foot (hallux) during whole test in male volunteer, 22-year-old under and after consumption of 400 ml 37.5 % vodka, corresponding to 150 g alcohol (P3, test 4). One dot corresponds to the mean of 3 consecutive measurements taken 5 min apart.

Figure 13 shows lactate in left foot (hallux) during whole test in male volunteer, 29-year-old under and after consumption of 400 ml 37.5 % vodka, 150 ml 35 % rom and 250 ml 4.6 % beer,

corresponding to 176.5 g alcohol (P1, test 4). One dot corresponds to the mean of 3 consecutive measurements taken 5 min apart.

Figure 14 shows lactate in left foot (hallux) during whole test in male volunteer, 28-year-old under and after consumption of 400 ml 37.5 % vodka, 100 ml 35% rom and 500 ml 4.6% beer,

5 corresponding to 159 g alcohol (P2, test 4). One dot corresponds to the mean of 3 consecutive measurements taken 5 min apart.

Figure 15 shows lactate in left foot (hallux) during whole test in male volunteer, 49-year-old under and after consumption of 1400 ml red wine of 13.5 %, corresponding to 196 g alcohol (P5, test 4).

One dot corresponds to the mean of 3 consecutive measurements taken 5 min apart.

10 Figure 16 shows lactate in left foot (hallux) during whole test in female volunteer, 43-year-old under and after consumption of red wine and drinks corresponding to 156.2 g alcohol (P6, test 4). One dot corresponds to the mean of 3 consecutive measurements taken 5 min apart.

Figure 17 shows lactate in left foot (hallux) during whole test in female volunteer, 49-year-old under and after consumption of red wine, corresponding to 97.5 g alcohol (P7, test 4). One dot corresponds

15 to the mean of 3 consecutive measurements taken 5 min apart.

Figure 18 shows absolute values of mean (S.D.) for all measurements before treatment, at $T_{\max}$ (max achieved effect at timepoint $T_{\max}$) and at time when effect disappeared. Columns from left to right; P1, P2, P3, P4, P5, P6 and P7.

20 Figure 19 shows relative values of mean for all measurements before treatment, at $T_{\max}$ (max achieved effect at timepoint $T_{\max}$) and at time when effect disappeared calculated as % of mean before treatment. Columns from left to right; P1, P2, P3, P4, P5, P6 and P7.

The figure numbers 20 and 21 and the table numbers 11-15 are not used in this application.

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Figure 22. Lactatogram from person (user) 8, before (grey squares) and 20 weeks with treatment (yellow triangles). 0 minutes corresponds to the start of reading. At 10th minute the person had taken active drinkable for the very first time and profound reduce in capillary lactate could be seen during following 70 minutes.

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Figure 23. Capillary lactate in right hand of P1 for 3 days with treatment (0-3877 min), 1st day without treatment (4319 – 5097 min), day 6 and day 7 without treatment (14399 – 16844 min) and day 1 and 2 after re-start of the treatment (17278 -18284 min).

Figure 24. Placebo-test: symptoms burden, individual data during test course, N=6: Active drinkable in 20 – 110 weeks before test + 3 days; quenched drinkable for 5-22 days and back to active drinkable for 5-22 days: Remaining percent of symptoms was calculated from individual start score before treatment.

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Figure 25. Placebo-test: fatigue presence, individual data during test course, N=6: Active drinkable in 20 – 110 weeks before test + 3 days; quenched drinkable for 5-22 days and back to active drinkable for 5-22 days. Remaining % of fatigue calculated from start score before treatment.

10 Figure 26. Placebo-test: A- mean of remaining symptoms and B- mean of remaining fatigue presence, both for N=6: Active drinkable in 20 – 110 weeks before test + 3 days; quenched drinkable for 5-22 days and back to active drinkable for 5-22 days. Remaining percent of symptoms was calculated from individual start score before treatment.

15 Figure 27. Lactatogram from person (user) 7, before (grey squares); 20 weeks with treatment (yellow triangles) and after 22 days on quenched drinkable. 0 minutes corresponds to the start of reading. At 10th minute the person had taken active drinkable for the very first time and profound reduce in capillary lactate could be seen during following 70 minutes.

20 Figure 28A - Sleep efficiency improvement during 120 weeks of treatment with active drinkable in P3; Figure 28B – Night-by-night Sleep efficiency fluctuations during placebo-test schedule in P3.

Figure 29A – Sleep Onset Latency improvement during 30 weeks of treatment with active drinkable in P7; Figure 29B – Night-by-night Sleep Onset Latency fluctuations during placebo-test schedule in
25 P7 (from day 36 P7 was on 20% lowered dose of oxalates in active drinkable).

Fig. 30. Effect of treatment of patients with chronic CFS/ME given active drinkable (oxalate) as measured by score on the list of Canadian Criteria as mean of remaining symptoms as % from start.

30 Fig. 31. Effect on CFS as measured by decrease in remaining score on Fatigue Scale schema (FS) in patients given active drinkable (oxalate).

The tables 17-22 are shown on the pages after figure 31.

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Example 1 – Active compound

We have shown that compositions containing certain amounts of oxalate or oxalic acid have an effect on CFS/ME/SEID. The active compound of the present invention has been given to the subjects as a component of a drinkable solution, naturally occurring in raw ingredients, not artificial or added. 250 ml drinkable solution were given 50 minutes before physical exercises (Example 2) or 720 minutes after the alcohol intake (test 3-4) or twice at 645 and 910 minutes after alcohol intake (Test 2). In Test 2-4 only active drinkable solution was given, while in Example 2 both variants of active and quenched drinkable solutions were given to the same person at different tests days. All drinkable solutions were given as 250 ml dose, corresponding to 152.5 – 177.5 mg soluble oxalates or oxalic acid- The range is due to seasonal (measured in November 2017 and December 2016) or naturally variation of oxalate and oxalic acid contents in raw ingredients.

To check the effects of a similar composition with significantly lower concentration of soluble oxalates, we have prepared a “quenched composition”. The term “quenched composition” is used in order to indicate that we actually have lowered concentration of soluble oxalates or oxalic acid in the active composition by chemical transformation of soluble oxalates into insoluble. Insoluble oxalates are crystals, which are insoluble in water and thus, have reduced capacity to be absorbed into a blood stream, and therefore, potentially cannot have any therapeutic effect. The active drinkable solution has been added 0.5 g calcium carbonate (CaCO_3) to one liter. The reaction resulted in formation of insoluble oxalate crystals, which are formed from any type of soluble oxalates present in active drinkable solution as a result of exchange between carbonate group of calcium carbonate to oxalate. By any type soluble oxalates we mean soluble oxalates with solubility in water higher or equal to that for calcium oxalate. When we use the term “oxalates” in a text, we also include all oxalates and oxalic acid. In HPLC system they will give the same peak and thus, could not be distinguished.

Preparation of the “drinkable” and “quenched drinkable”

Active drinkable was prepared by mixing the fruits, greens, vegetables and nuts in proportions necessarily to achieve desirable concentration of soluble oxalates in a final product – active drinkable. The desirable concentration was determined experimentally in order to have therapeutic effect on symptoms relief in subject 1, which suffer of ME/SEID/CFS. For that active drinkable solutions with graded doses of oxalates were consumed at prescribed times during a day: each time a new dose, in increased order. The best dose was tested for additionally couple of weeks to confirm the long-term persisting therapeutic effect. The desirable dose of oxalates was determined as minimal dose taken in one portion drinkable solution which gave therapeutic effect during 5 consecutive hours on pain relief

as short term-effect, and for at least for 14 consecutive days as long-term effect, and did not exceed the daily acceptable dose for oxalic acid.

To see if therapeutic effect was associated with concentration of oxalates in a drinkable, a number of recipes with alternative raw ingredients were tested (Table 2). For that raw ingredients were chosen from the published anywhere (Hönow & Hesse, 2002) in literature concentration of oxalates and balancing the recipe in respect to other nutritionals and sugars, so the nutritional values were as much equal as possible for all recipes. The therapeutic effect was tested experimentally on subject 1 as described above.

Quenched drinkable was prepared according to the same recipe as active drinkable solution, when 0.5 g calcium carbonate (CaCO_3) was added and mixed properly. Excessive formation of CO_2 evidenced for the successfully performed exchange between carbonate and oxalate groups and crystal formation of insoluble oxalates. Quenched drinkable was used to evidence the dose-dependence of a therapeutic effect and by that distinguishing the placebo from the real effect. The tastes, appearance, fragrance, colour of the quenched and active drinkable solutions were not distinguishable by humans. The crystals were suspected to the FTIR spectra to confirm the structure of the reaction product.

Chemical composition of analyses of the “drinkable” and “quenched drinkable”

We describe in details below how we quench the active drinkable in order to obtain the quenched solutions.

In Tab. 1 the results of chemical composition of drinkables are reported as mean value of 10 randomly chosen liters from production batch of 160 liters. The amount of oxalate is not indicated in the table 1 below and discussed later. The results in Tab. 1 show that differences in measured values were not significant, rather due to analytical variation than real differences. It is important to emphasize that amount of sugars and energy value was almost the same in those two drinkable solutions. The only significant differences (marked with *) were documented for the amount of calcium, thus 0.5 g of calcium carbonate (CaCO_3) was added to quench the drinkable (described in detail below); ** - for magnesium and *** - for iron. All analysis of nutritionals were performed at German Institute of Food Technology, according to accredited internal and external methods as given in table. Accreditation is valid for methods marked with A.

Table 1. Nutritional composition of two drinkable solutions: active and quenched.

Parameter	Calculated as	Method	Measured value in a dose of 290 g quenched drinkable with no therapeutic effect	Measured value in a dose of 290 g drinkable with therapeutic effect	Units
Moisture		DIL256-1A	259,84	267,96	g
Ash		DIL259-2A	1,19	1,13	g
Raw Protein	N*6,25	L17.00-18A	1,51	1,57	g
Total Fat		DGF C-III 19 (00)A	1,02	1,04	g
Carbohydrates		Calculation	24,59	24,21	g
Fiber		L00.00-18A	2,47	2,76	g
Sucrose		DIL789-9A	<0,58	<0,58	g
Glucose		DIL789-9A	8,47	8,38	g
Fructose		DIL789-9A	16,12	15,83	g
Maltose		DIL789-9A	<0,87	<0,87	g
Lactose		DIL789-9A	<0,87	<0,87	g
Sugar, sum		Calculation	24,59	24,22	g
Ascorbic acid		QMP_504_K L_52_020A	46,98	50,17	mg
Thiamine		DIN EN 14122:2010 A	0,06	<0,03	mg
Riboflavin		DIN EN 14152:2006 A	0,15	0,15	mg
Niacin		USP 34. Method 441	0,75	0,81	mg
Pyridoxine		DIN EN 14663:2006 A	0,23	0,23	mg
Folate		DIN EN 14131:2003	0,09	0,10	mg
Tocopherol		VO (EG=152/2009, IV, B)	1,16	1,04	mg
Saturated fat	Triglyceride	DIL770-16A	<0,29	0,41	g
Monosaturated fat	Triglyceride	DIL770-16A	<0,29	<0,29	g
Polysaturated fat	Triglyceride	DIL770-16A	0,70	0,52	g
Sodium	Na	DIL828-8A	<0,06	<0,06	g
Salt	Na*2,5	Calculation	<0,58	<0,58	g
Phosphorous	P	DIL1014-5A	0,04	0,04	g
Potassium	K	DIL938-9A	443,70	452,40	mg
Magnesium	Mg	DIL937-9A	1,45**	27,09**	mg
Calcium	Ca	DIL931-9A	1191,90*	475,60	mg
Iron	Fe	DIL962-6A	1,07***	2,67***	mg
Zink	Zn	ICP-OESA	<0,58	<0,58	mg
Copper	Cu	DIL940-5A	<0,58	<0,58	mg
Manganese	Mn	DIL1015-5	0,41	0,44	mg
Selenium	Se	DIN EN 15763, mod. /F	<0,58	<0,58	mg
Energy value		Calculation	501,70	498,8	kJ
Energy value		Calculation	118,90	118,90	kcal
Cholesterol		L20.01-13A	<2,9	3,48	mg

Levels of soluble and insoluble oxalates in active drinkable and quenched drinkable solutions

Methodology. To ensure that therapeutic effect was dose-dependent only on oxalic acid and oxalates, also content of other organic acids in drinkable solutions were investigated.

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Concentration of oxalates, oxalic acid and other organic acids were measured by HPLC internal standard method at Synthetica AS, Oslo, Norway to assess for content in the different recipes and in active and quenched drinkable. Oxalic acid (Fluka, cat. Nr.75688 lot no 1192734), L-tartaric acid (Aldrich, 25, 138-0), Malonic acid (Fluka, 63301), DL-Malic acid (Fluka, 02308), Citric acid (Merck, 79807-1) were used as external standards. Drinkable solutions were centrifuged at 4000 rpm for 10 min and supernatant collected and centrifuged for the second time. The sample was filtered through a 0.45 µm syringe filter followed by second filtration through a 0.2 µm syringe filter, and analyzed by HPLC. HPLC conditions were as following: ACE 5 C18 column with 250 mm X 4.6 mm i.d. (Part. No. ACE-121-2546) connected to Agilent Infinity 1260 quantifying HPLC system with detector DAD, 10 mm flow cell. Detection at 214 nm at flow rate 0.7 ml/min and with 50 mM phosphoric acid (sodium) buffer solution, pH 2.8 as mobile phase.

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Water (VWR, 23595.328, lot. Nr. 17B174005, and HCl (Sigma Aldrich, 30721, STBH0830) were used in preparation of the samples for quantification of soluble oxalates in drinkables. For that 50 ml of each sample was accurately diluted three times and transferred to a 250 ml flask, by using 100 ml of water, HPLC quality. Quantification of *soluble oxalates* was performed on supernatants *of active drinkable and quenched drinkable* produced after centrifugation as described above. Calculated difference between those two values gave calculated value for fraction of soluble oxalates transformed into insoluble oxalates by treatment with CaCO₃. Quantification of total oxalates was performed on supernatants of the samples treated with HCl prior to centrifugation, modified from Al-Wahsh (2012). For that 50 ml of each sample was accurately diluted three times and transferred to a 250 ml flask, by using 10 ml of 2N HCl. The samples with HCl were further incubated at 80°C for 30 minutes with vigorously shake from time to time, equal for all samples. Insoluble oxalates were calculated as difference in concentration of soluble from total oxalates. The HPLC conditions were as following: Qualified Instrument Agilent Infinity 1260 with Open Lab Chemstation, ACE 5 C18 column with 250 mm X 4.6 mm i.d. (Part. No. ACE-121-2546) at 15°C, injection volume of 3 µl and gradient of A: 50 mM phosphoric acid (sodium) buffer solution, pH 2.8 and B: 100% CAN as mobile phase. Detection through 10 mm flow cell at 214 nm. Gradient table: start 100% of A; 15 min – 100 % A; 16 min – 5 % A and 95 % B; 25 min – 5% A and 95% B and 26 min – 100% A, at 0.7 ml/min flow. The column

was washed with CAN for 10 min to ensure elution of potential non-polar compounds in the samples between the runs.

Duplicate standard solutions of oxalic acid were prepared in five different concentration levels for use as external calibration standards: preparation I in the range of 0.06 – 1.02 mg/ml and preparation II – 0.07 to 1.03 mg/ml. The slope (2268.7) from the calibration curve was used for calculation of oxalate in the samples according to formula:

$$C_{\text{oxalic acid}} \left(\frac{\text{mg}}{\text{ml}} \right) = \frac{\text{Peak area oxalic acid}}{\text{Slope reference standard}}$$

The same formula and approach was used for quantification of any other organic acid.

Results. Quantification of organic acids, including L-tartaric, Malonic, DL-Malic and Citric acid was performed by comparing the peak areas (Figures 1 and 2). Concentration of oxalic acid was most affected by this treatment. This was in compliance with known action of CaCO_3 , which first react with the strongest acid in the mix solution – here, oxalic acid. Mean value of measured concentrations of soluble oxalates in 8 randomly chosen untreated with HCl samples of active drinkable was 0.71 ± 0.04 g/L oxalate (or corresponding to oxalic acid anions in HPLC system). This is corresponding to 177.5 mg per dose of 250 ml drinkable. Seasonal variation of soluble oxalate content was documented in active drinkable: 177.5 mg per dose (ingredients are from Italy, November 2017, Tab. 2) and 152.5 mg per dose (ingredients are from Norway and Italy, December 2016, Tab.2).

Concentrations of soluble oxalates were measured in different recipes two times to exclude significant seasonal variation (Tab. 2). The lowest concentration of soluble oxalates was measured in 6-

Quenched drinkable, followed by recipe 3-Rhubarb and 1-Strawberry. The highest concentrations were measured in 5-Active drinkable and 4-Banana. Presence of satisfying and long-lasting therapeutic effect was experimentally confirmed only for recipe 5-Active drinkable. Effect from 4-Banana was unpleasant and too tough, while effect from the 3-Rhubarb was unpleasant and effects from both were not lasting long enough either on the short-term of 5 hours or on long-term of 14 days.

There was no or reduced effect from the 1-Strawberry drinkable, despite that concentration of soluble oxalates was in the same range as for 5-Active drinkable: 0.69 vs 0.61 mg/L. At least three parameters, which we did not solved in this attempt, could explain the reduced or lack of effect from 1-Strawberry: the ration between soluble and insoluble oxalates and types of soluble oxalates and ratio between them. Quantification of the total oxalates in the solutions after treatment with HCl failed. However, the concentration of remaining in solution soluble oxalates after treatment with

CaCO₃ and before treatment could be compared. *The calculated ratio soluble:insoluble* in 1-Strawberry was 1.5, while in 5-Active drinkable the corresponding ratio was 1.9. This ratio somehow mirrors the composition of types of soluble oxalates in different recipes.

- 5 We concluded that to achieve and maintain a pleasant therapeutic effect with satisfying pain relief and long-term effect *the concentration of soluble oxalates should be* above 0.39 mg/L as in 3-Rhubarb but less than 0.87 mg/L as in 4-Banana. Additionally, ratio between soluble and insoluble oxalates might have influence on the therapeutic effect. Because, therapeutic effect was documented only from 5-Active drinkable and not from 1-Strawberry, we conclude that the ratio between soluble and
- 10 insoluble oxalates should have influence on the therapeutic effect. Moreover, one important detail was not possible to solve experimentally, but which has significant impact on the therapeutic effect – *types of soluble oxalates and ratio between them*. It is not possible to distinguish between oxalates by HPLC analysis and therefore this work should be done experimentally on the subject 1 in a future, by testing different combinations of different types of soluble oxalates in a mixture. Development of
- 15 special analytical tools will also be an option. At this moment, such methodology is not available to us. We conclude that at least four parameters impact the therapeutic effect of a drinkable: concentration of soluble oxalates (1); ratio between soluble and insoluble oxalates (2); types of soluble oxalates (3) and ratio between different types of soluble oxalates (4).
- 20 Remaining concentration of soluble oxalates in 6-Quenched drinkable, which is the same as 5-Active drinkable but after the treatment with CaCO₃, was 0.27 mg/L in November 2017 and 0.18 mg/L in December 2016. Thus, confirming that treatment with CaCO₃ in November 2017 gave lowering of the soluble oxalates by 56 %. This drinkable was used in placebo-test.

Table 2. Oxalate and oxalic acid concentrations in samples of different recipes tested for presence of therapeutic effect. The first value is from November 2017 and in parenthesis those are from December 2016. * - two drinkable solutions: active drinkable and quenched drinkable.

I.D. of drinkable	Therapeutic effect (yes/no) of untreated drinkable	Soluble oxalates in untreated sample, g/L	Remaining Soluble oxalates in quenched drinkable, g/L after Treatment with CaCO ₃	Calculated Fraction of Insoluble oxalates produced due to treatment with CaCO ₃ (precipitate suspected to FTIR analysis), g/L	Amount of soluble oxalates in 250 ml drinkable, mg
1-Strawberry	no	0.69 (0.92)	0.24 (n.d.)	0.45 (n.d.)	172.5 (230.0)
3-Rhubarb	yes, not lasting	0.39 (0.16)	0.12 (n.d.)	0.27 (n.d.)	97.5 (40.0)
4-Banana	yes, not lasting, unpleasant effect	0.87 (1.04)	0.40 (n.d.)	0.47 (n.d.)	217.5 (260.0)
5-Active* Spinach	Yes, long-lasting	0.61 (0.71)	0.27 (0.18)	0.34 (n.d.)	152.5 (177.5)
6-Quenched* Spinach	no	Treated with CaCO ₃	0.27 (0.18)	0.34 (n.d.)	68.5 (45.0)

5

Analyses of the spontaneously formed precipitate and crystals produced during treatment with CaCO₃

Processing and methodology. Batch of 160 drinkable doses of 250 ml was produced at German Institute of Food Technologies (DIL) with help of High Pressure Processing (HPP) technique. High pressure treatment was carried out in a batch, 55-L-industrial unit (Wave 6000/55, Hiperbaric, Burgos, Spain). Freshly made drinkable was portioned into 250 ml plastic PET bottles and treated at 600 MPa for 3 min holding time. Bottles were kept at 7±1°C until chemical and microbiological analyses were performed. Bottles were subjected to microbiological examination each second week. Microbial analyses were performed at DIL on total viable count, yeast and molds. In addition, the colour was measured (L*, a* and b* values, Konica Minolta Spectrophotometer CM-600D at 20°C and standard illuminate light source D65). For cell enumeration, collected samples were serially diluted in Maximum Recovery Diluent CM733 (Oxoid, Deutschland GmbH, Wesel, D.) and surface-plated onto different culture media. After incubation, plates were counted and the results expressed as cfu/ml. Detection limit was 10 cfu/ml. The microbiologic analyses were all accredited.

20

Test for therapeutic effectivity during self-life of 6 weeks. Each bottle containing 250 ml of drinkable were consumed by a subject 1 accordingly to the treatment schema. The symptoms, stamina

and cognitive performance were self-observed and self-reported at least during 8 time points during a day. This experiment take place during week 130 to 133 after start of CFS/ME/SEID treatment, and at this time user was in a good physical and cognitive form and reported minor number of symptoms.

Each time before consumption of the dose, the bottle was examined in a good light for any

5 deterioration signs.

Analysis of crystalline powder spontaneously formed during the storage. Crystals spontaneously formed during the storage of the HPP-treated drinkable were washed out as described in Da Costa et al (2009) and dried prior analysis. The same washing procedure was performed on crystals formed during the reaction of active drinkable with calcium carbonate (CaCO_3). Analysis were performed at Department of Chemistry at University of Bergen, The Norwegian NMR Platform, Norway. The samples were analyzed at Laboratorium for FTIR spectroscopy and chemometry at University of Bergen. The FTIR spectra of the three samples were compared with a sample of CaC_2O_4 (calsimum oxalate).

15

Storage experiment of active drinkable used in treatment. Freshly made drinkable of oxalate mix was analyzed as described earlier, in the same HPLC system, and then stored at 4-7°C for one week before the HPLC quantification was performed again. All analyses were performed by Synthetica AS, Oslo, Norway. Three randomly chosen liters from production of 70 liters had been analyzed. Each sample was storage in 6 aliquots of 50 ml each in a glass bottles with a tight cap: 3 samples were analyzed untreated to attempt content of soluble oxalates and 3 samples were treated with HCl prior to HPLC to attempt the total oxalates in a sample.

20

Results

The therapeutic effect was tested by subject 1 and was present until day 21, and approximately from day 19 began gradually deteriorates. Less effect was observed and reported as increased pain in muscles and skeleton, chills, strong headache/migraine, frequent nocturnal urination, tender lymph nodes on the neck and under arm holes, sore throat, flu-like symptoms and malaise, sleep disturbances and post exertional malaise. The symptoms appeared suddenly on day 19th and increased in numbers and severity during following days. At day 21 the situation was not acceptable to tolerate and this type of drinkable was exchanged with freshly made. All symptoms disappeared during first 5 hours after intake of the freshly made drinkable.

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Approximately after 14 days some light precipitate was seen at the bottom of each bottle (Photo in figure 3). The most of precipitated was observed after day 19th and amount of it continued to grow for additionally 30 days until formation of more substance was not observed anymore.

Evaluation of the colour difference ($\Delta E=1,0-2,0$) dependent on storage period after HPP treatment showed “subtly seen difference”. Aerobic total count (TPC) was at the level of 10^3 cfu/ml after the pressure treatment. The natural occurring yeast and molds concentration was reduced down to the detection limit (<10 cfu/ml). In Table 3 the results of further examinations are collected.

Table 3. Microbiology before and after HPP treatment.

Active drinkable	HPP treatment			
Storage at $7\pm 1^\circ\text{C}$, days	1	14	28	42
pH-value	4,15	n.d.	4,34	n.d.
Aerob mesophile total bacteria count (cfu/ml)	$7,3*10^3$	$1,0*10^4$	$4,6*10^3$	$2,2*10^3$
Yeasts (cfu/ml)	<10	<10	<10	<10
Molds	<10	<10	<10	<10

Results of the microbiological examinations confirmed that under storage the drinkable was sterile and no microbiological activity of the bacteria, yeasts or molds could be found. Therefore, the observed precipitated was suspected to have a chemical nature, more specifically – slow rate exchange between calcium and soluble oxalates to form insoluble calcium oxalate.

Crystals collected from the bottles of 5-Active drinkable (Photo in figure 3) had been suspected to the FTIR analysis, along with crystals formed during treatment with CaCO_3 from 6-Quenched drinkable solution. Both samples, displayed the same features as calcium oxalate, with vibration bands at 1600 cm^{-1} (C-O stretching), 1315 cm^{-1} (C-C stretching), 777 cm^{-1} , 660 cm^{-1} , and 511 cm^{-1} . Thus, we conclude that these samples are in fact calcium oxalate.

Thus, conclude from the FTIR spectra (3.3), the main compound of the insoluble powder from reaction with CaCO_3 was calcium oxalate. Consequently, the fraction of soluble oxalates in untreated samples most likely corresponds to all possible oxalates, which are more soluble in water than calcium oxalate. Magnesium oxalate is 149 times more soluble in water than calcium oxalate, and iron (II), ferrous oxalate is 12 times more soluble than calcium oxalate.

Additionally, we have also conducted HPLC analysis of the Active drinkable versus Quenched drinkable used in Placebo-test and Example 2 (Post exercise). Only the first peak with retention time 3.77 min differ in those chromatograms. Overlaid chromatograms confirm the expectation that the peak corresponds to oxalic acid (anion), e.g. oxalates or oxalic acid. Slope for calculation of organic acid content is given in Table 4 and calculated concentration in samples is given in Table 5.

Table 4. Slope for calculation of organic acid content

Reference acid	Retention time	Conc. I (mg/ml)	Conc. II (mg/ml)
Oxalic acid	Approx. 3.77 min.	1,05	1,56
L-Tartaric acid	Approx. 4.44 min.	1,08	1,53
Malonic acid	Approx. 6.61 min.	0,99	1,71
DL-Malic acid	Approx. 6.35 and 13.32 min*	1,27	1,68
Citric acid	Approx. 14.56 min.	1,96	1,46

*Two peaks

Table 5. Concentration of soluble oxalates in different types of mixes of drinkable measured for first time, December 2016.

Sample	Area Oxalic acid	Calculated concentration of oxalic acid (mg/ml)	Calculated amount of oxalate anion in 250 ml portion of active drinkable mg
Sample Ø_F	602,5	0,71	178
Sample Ø_U	150,8	0,18	45
Sample B	886,7	1,04	260
Sample J	785,1	0,92	230
Sample R	138,2	0,16	40

Conclusion. The reaction of active drinkable and 0.5 g CaCO_3 results in an exchange between CO_3^{2-} group on $\text{C}_2\text{O}_4^{2-}$ group with formation of insoluble precipitate of calcium oxalate (FTIR spectra), simultaneously as level of soluble oxalates in Active drinkable (Fig. 14) is reduced by 56% (November 2017) or 75% (December 2016). Therefore, we conclude that therapeutic effect of naturally oxalates is firstly associated with presence of necessarily amount (dose) of soluble oxalates. Soluble oxalates, which will exchange the $\text{C}_2\text{O}_4^{2-}$ group with CaCO_3 can be anything among given in Tab. 12 with water solubility equal to calcium oxalate and above.

Storage experiments

Storage experiments were performed on 5-Active drinkable solution at day of production and one week later. Among 3 analysed samples (liters), only one sample demonstrated the expected pattern in oxalate transformation. The reason for that was the huge experimental insecurity and methodological difficulties in transfer and reduction of samples from 1000 ml to 50 ml. Perhaps, insoluble crystals were not evenly distributed and consequently transferred to the storage bottles. However, we succeeded to demonstrate it in one of three samples and with regard that values were produced from separate treated samples, they are in very good agreement with each other. We documented: decrease in soluble oxalates by 9 mg, increase in total oxalates by 7 mg and increase in insoluble oxalates by 16 mg per portion of 250 ml active drinkable solution. It was earlier concluded that dose of soluble oxalates in one portion active drinkable should be more than 97.5 mg (3-Rhubarb) and less than 217.5 mg (4-Banana) and that there were 55 mg less soluble oxalates per portion of 250 ml in 3-Rhubarb than in 5-Active drinkable (Tab. 2). Subject with ME/CFS/SEID takes 250 ml drinkable 4 times a day and consequently, getting 36 – 64 mg soluble oxalates less per day available when using a drinkable

produced for more than one week ago. This confirmed, what we experienced in practice – active drinkable was less effective already after 1 week of storage in home refrigerator.

5 Example 2 - Reduction of lactate load in healthy person post exercise

We have found that the compositions of the present invention reduce the amount or concentration or time with the presence of lactate above normal level (Total lactate load over the time) of lactate in the blood of healthy persons. This is a universal and general effect, i.e. the level of lactate will be reduces
10 either the subject has a disease with a high level of lactate or is a healthy person where the level of lactate are higher than normal. The test persons in the example below have exercised in order to obtain a high level of lactate in the blood. We anticipate that high levels of lactate can be reduced with the composition of the present invention independent of the cause of the high level. The composition of the invention will also inhibit an increase in the lactate level since it has a general lactate reducing
15 effect. The composition can thus be used as a preventive measure to impede high lactate levels.

Normal values of lactate in human blood is within the range of 0.5 to 2.0 mmol/L. Lactate clearance in healthy persons is organised via Gori cycle in liver (60% of clearance), kidneys (30%) and other organs and tissues, such as heart, muscles, intestine. During Gori cycle, lactate transported from
20 working organs and muscles into liver cells, where it transforms to pyruvate, which then stored in a form of glucose. Glucose, if it is needs for energy, transported back to muscles or other activated tissues, when it undergoes chemical transformations to give rise to the key compounds of energy producing TCA cycle. The energy stored in form of phosphate bonds of ATP molecules. 38 (36) molecules of ATP are produced from two glucose molecules during TCA cycle. Released from
25 phosphate bonds energy, used for cognitive and physical performances (job) of the body.

Monitoring of lactate levels in a routine clinical practice is not widely spread, probably because: (1) it presents in all cells (except for the mature erythrocytes); (2) levels are increased under physical exercises; (3) levels are normally very strictly regulated, and abnormal levels associated with life
30 threatening conditions are only slightly above the normal range. However, some health conditions, where monitoring of lactate levels are useful, could be listed. They are all associated with hyperlactatemia. Hyperlactatemia is a life treating condition, when levels of lactate in a blood are above 2.0 mmol/L with or without the presence of lactic acidosis or with or without the disturbed in lactate-to-pyruvate ratio.

35

In several clinical conditions, admission hyperlactataemia has been demonstrated to be a predictor of death or outcome in: children with sepsis (Duke et al., 1997); cardiac surgical patients (Khosravani et al., 2009); trauma/neuro patients (Khosravani et al., 2009); shock or respiratory and renal failure (Juneja et al., 2005); ruptured abdominal aortic aneurysm repaired (Singhal et al., 2005), to mention some. Another group of conditions where hyperlactatemia is direct course of the death is innate hereditary metabolic disorders. Some examples are: mitochondrial encephalomyopathy, pyruvate carboxylase deficiency; succinyl-CoA ligase deficiency; mitochondrial hepatoencephalomyopathy. Course of the death at such conditions is decreased clearance or increased production of the lactate as a result of biochemical disturbances in pathways or as result of misbalance caused by treatment.

Our own data described in a co-pending patent application shows that also ME/CFS/SEID and Fibromyalgia are within the same group of conditions, characterized by increased Total Lactate Load.

To our knowledge, a medicinal pharmacological treatment against hyperlactatemia (with or without lactic acidosis and disturbed lactate-to-pyruvate ratio) does not exist. The widely spread clinical practice described in literature called "Lactate guided therapy" has following therapeutic targets: optimizing mean arterial pressure by fluid isotope administration; multi-organ protection by early enteral nutrition; optimizing metabolic control by means of insulin infusion therapy; prevention/treatment of infections.

Composition given to healthy persons

Single dose of 250 ml mix of drinkable oxalates from naturally food sources was used to demonstrate general effect of reducing Total Lactate Load in healthy persons after exercise. The drinkable oxalates are described in example 1.

Participants

Sixteen volunteers had been tested. All persons self-reported that they did not have any chronic health issues. Some of them exercised on daily or weekly basis, and some did not.

Exercise

No special instructions were given before the test and participants could keep their daily routines and responsibilities. However, some dietary restrictions have been given: avoid foods with high content of calcium, including milk and milk products, cheese and nuts, alcohol, coffee and tea for minimum 60 minutes before intake of drinkable.

Each test was performed twice on the same person, with less than 14 days between. Participants were randomly selected to get active drinkable or quenched drinkable 50 minutes prior to exercise. All participants consumed one 250 ml dose of drinkable, either active drinkable or quenched drinkable (see example 1). The next time person get the opposite drinkable solution, so effect of both drinkable solutions were tested. Test persons did not knew which type of drinkable they were given, nor did the testing person. It was also unknown to participants, which parameters were measured in the blood.

Dependently on the physical condition of the person, the exercise conditions on the treadmill were settled. The same individual program was repeated both days. Warming up by going 5 minutes at 6 km/h was the same for all, following by running for 5 minutes at individual speed between 8 -15 km/h. Relaxation in a chair for following 172 minutes and a glass of water after exercise was mandatory for all.

Measurements of lactate

Lactate levels are measured by mobile tester Lactate Scout+ from EKF Diagnostics (Germany) for self-monitoring. Fingertip or hallux-tip was cleaned, dried and punctured by Microlet lancett fra Bayer (Germany) and 0.2 µl whole capillary blood was absorbed into Lactate Scout Sensors from SensLab GmbH (Germany). Results were manually registered in electronic format, with additional confirmation by screenshots of the monitor by iPhone-6S.

The monitoring was undertaken with varying, none rhythmical intervals to avoid unknown periodic cycles in the lactate production. The time for measurements was the same for each tested person.

Calculation and statistics

Total Lactate Load was calculated as Area under the curve (AUC) defined by time points of 50, 66, 71, 82, 102, 126 and 232 minutes post intake. AUC was calculated with trapezoidal rule and according to the formula:

$$\int_a^b f(t) dt = \sum_{k=1}^n \frac{f(t_{k-1}) + f(t_k)}{2} \Delta t_k$$

were t_k is the time when the k -th measure was performed and $f(t_k)$ is the corresponding concentration value, i.e. the first measure of the concentration value $f(t_0)$ is taken at the time t_0 , the next $f(t_1)$ is taken at the time t_1 , incremented until the last measure $f(t_N)$ is taken at the time t_N . $\Delta t_k = t_k - t_{k-1}$ is the length of the k -th subinterval, i.e. time difference between two measures k and $k-1$.

Therapeutic effect was calculated as % reduced AUC according to the formula:

$$x = \frac{\text{AUC } t \text{ (Active drinkable)} * 100}{\text{AUC } t \text{ (Active drinkable + CaCO}_3\text{)}}$$

where AUC t is Area Under the Curve of Lactate measurements defined by same time point for test with Active drinkable and Active drinkable with excess of CaCO₃ and Active drinkable with excess of CaCO₃ is the same as 6-Quenched drinkable in all other tests, also in co-pending patent. Paired T-test in Excel was performed on data from the same person consumed test drinkables, and T-test between groups consumed one or another drinkable.

Results

Physical restitution with active drinkable

We have (placebo-test in ME patients in co-pending patent application) shown the lack of prolonged therapeutic effect of quenched drinkable. Quenched drinkable is the active drinkable with reduced concentration of soluble oxalates, but same contents and composition of sugars.

Totally 16 healthy volunteers have been tested. Thirteen of them demonstrated better effect of Active drinkable, i.e. lower levels of lactate, while 3 volunteers had better effect of Active drinkable with excess CaCO₃. A typical lactatogram for a representative person of the first group is shown in Figure 4.

Thirteen of 16 volunteers had better effect of Active drinkable without CaCO₃, (81 %). The effect demonstrates time-dependence: increase of therapeutic effect from 50 minutes post intake, clear individual maximum at different time point (Table 6) and decrease afterwards (Fig. 5). Increase of therapeutic effect occurred within 50 to 232 minutes post intake and was individually presented. The maximum achieved reduction of Total Lactate Load was within the range of 7.2 to 33.1 % (Table 6).

This group clearly divided into two sub-groups: one with strong response of 23.1 ± 7.0 % reduction of AUC and one with moderate effect of 9.0 ± 1.1 %.

Table 6. Therapeutic effect of one drinkable dose of 250 ml corresponding to 152.5 – 177.5 mg of soluble oxalates in totally 16 healthy volunteers.

I.D.	Gender	Highest achieved	Speed, km/h	Exercise routines	Drinkable with best	Mean effect	% of population
14	F	15.9	12.0	0/7	AD+CaCO ₃	28.2±12.9	19
17	M	27.0	10.0	5/7	AD+CaCO ₃		
20	F	41.6	10.0	0/7	AD+CaCO ₃		
1	M	25.3	12.0	7/7	AD	23.1±7.0	50
2	F	26.0	12.0	4/7	AD		
6	M	19.5	15.0	3/7	AD		
4	F	12.1	10.0	1/7	AD		
15	F	23.0	8.0	1/7	AD		
9	F	30.1	12.0	5/7	AD		
7	M	15.9	16.0	7/7	AD		
18	F	33.1	10.0	5/7	AD	9.0±1.1	31
19	M	9.2	13.0	2/7	AD		
5	F	7.2	10.0	2/7	AD		
8	M	9.9	12.5	0/7	AD		
3	M	9.5	10.0	0/7	AD		
11	M	9.4	14.0	4/7	AD		

Three of 16 persons had better effect of Active drinkable with excess of CaCO₃, corresponding to 19 % of totally tested (Fig. 6 and Table 6). The effect was time-dependent from the intake of drinkable with maximum reduction at 126 min (in 2 of 3 persons) and 102 min post intake in one of 3 persons (Fig. 7). The maximum achieved reduction of Total Lactate Load was within the range of 15.9 to 41.6 %.

Summarised data and statistics are collected in Tab. 7 and 8. Mean age for group with best response to Active drinkable was 44 ± 7 years, with distribution between genders 7:6 (M:F), Tab.2. Mean AUC₂₃₂ for Active drinkable with CaCO₃ was 579.8 ± 99.3 mmol/L/min, and 489.9 ± 114.8 mmol/L/min for AUC₂₃₂ for Active drinkable. Paired test P-values for the same person were < 0.05 (95% probability)

in all persons, except five. T-Test between treatments was highly significant with P-value of 0.00049, which corresponds to 99.9% probability that the results is not occurred by chance.

Mean age for persons responded best to Active drinkable with CaCO_3 was 38 ± 12 years, with 1 male and 2 females, Tab.7. Tab.8. Mean AUC_{232} for Active drinkable with CaCO_3 was 284.8 ± 95.1 mmol/L/min, and 392.6 ± 73.5 mmol/L/min for AUC_{232} for Active drinkable. Paired test P-values for the same person were < 0.01 (99% probability) in all persons. T-Test between treatments was significant with P-value of 0.0173, which corresponds to 99% probability that the results is not occurred by chance.

Table 7. Total Lactate Load (AUC) for 232 minutes post intake of the single 250 ml dose of the oxalate mix in 16 of 20 volunteers (81%), where effect of Active drinkable is more profound than Active drinkable with excess of CaCO_3 .

I.D.	Gender (M:F)	Age	Total Lactate Load (AUC_{232})		P-value of paired test between individual values
			QD	AD	
1	M	53	429.5	327.2	0.0182
2	F	52	628.4	480.4	0.0010
3	M	48	647.3	537.9	0.0449
4	F	43	538.7	473.5	0.1560
5	F	47	420.4	389.9	0.1271
6	M	34	606.7	579.6	0.3044
7	M	49	698.7	588.6	0.0467
8	M	42	610.9	608.3	0.4786
9	F	41	484.0	413.1	0.0157
11	M	28	760.0	700.5	0.0161
15	M	47	491.1	422.4	0.0044
18	F	45	570.6	383.6	0.0023
19	M	37	422.4	435.3	0.3922
mean	9:8	44	583.3	489.9	
S.D.		7	93.4	114.8	
t-test between groups				0.00053	

Table 8. Total Lactate Load (AUC) for 232 minutes post intake of the single 250 ml dose of the oxalate mix in 3 of 20 volunteers (15%), where effect of Active drinkable with excess of CaCO_3 was more profound than from Active drinkable.

I.D.	Gender (M:F)	Age	Total Lactate Load (AUC_{232})		P-value of paired test between individual values
			QD	AD	
14	F	26	500.2	572.9	0.0037
17	M	49	455.3	595.9	0.0007
20	F	38	337.3	512.5	0.0007
mean	1:2	38	284.8	392.6	
S.D.		12	95.1	73.5	
t-test between groups				0.0173	

Discussion and conclusion

In literature and clinical practice the Clearance and not Absolute values of the lactate referred as much more important parameters for prediction of the death or outcome in life threatening conditions associated with hyperlactataemia.

Total Lactate Load is the function of Clearance and reflexes the damaging effect of the Lactate overload over time, associated with severe and unpleasant experiences in the body. Total Lactate Load was in this work expressed as Area Under the Curve for lactate measurements over the time.

The goal for the anti-hyperlactatoemic therapy should therefore be not only decrease in absolute values, but rather reduction of Total Lactate Load, either through reducing the absolute values or restitution time or both, simultaneously. Reduction of high values or time used by the body to clear overloading levels will also reduce the AUC and by that Total Lactate Load. Practically, it means, less time with life threatening hyperlactatemia and consequently less pain and other unpleasant severe symptoms to the patient.

In this work, therapeutic effect of one dose of oxalate mix, corresponding to 152.5 – 177.5 mg of oxalic acid anions demonstrated to have profound effect on 81 % of tested healthy persons. Another 19 % responded better on lowered dose of oxalates, corresponding to 67.5 mg. The unveiled difference has no explanation at the moment. However, one of 6 persons with ME/CFS/SEID demonstrated better performance on lowered dose of oxalates in Placebo-test (P7). The practically output, however, indicate that treatment of the Hyperlactatoemia is possible in entire population. If distribution of documented responses is also truth for whole population, then it is 81 % chance for that person will respond better to oxalate mix or higher dose and if not, mix of oxalates with reduced dose could be used as second choice. Single dose became operative and effective within 50 minutes post intake and reduced Total Lactate Load by 7.2-33.1% and 15.9-41.6%, respectively, in mentioned groups. The effect prolonged during at least 232 minutes post intake. To ensure prolonged and more profound effect multiple dosing with intervals of 3- 5 hours (data from ME/CFS treatment) should be considered. T-test between treatment groups (AD vs AD+CaCO₃) were highly significant. Five of 16 individually paired tests at AUC₂₃₂ had been not significant (Tab. 7). The reason for that are the individual responses to the treatment which causes that maximum effect occurs at different times and it lasts for different periods of time, especially for the very first dose. In practise, it is much more additional tools to achieve higher effect than demonstrated in this experiment, such as

customization of the dosage to body mass, body fat %, body muscle weight and more frequently regiment.

Moreover, post exercise hyperlactataemia and increased Total Lactate Load in healthy persons are well known. There are no commercial remedies to reduce lactate for this group of healthy people. Also, overtrained athletes suffers of Hyperlactatoemia and will benefit from this treatment as restitution sports drink.

Finally, we believe that the mechanisms of lactate clearance in the body is universal and independent of the cause of hyperlactataemia and therefore, all conditions where hyperlactataemia is present should be treated with mixture of oxalates.

Ensamples of the Hyperlactataemia and/or lactic acidosis:

- Genetic conditions

- Biotinidase deficiency, multiple carboxylase deficiency, or nongenetic deficiencies of biotin;
- Diabetes mellitus and deafness;
- Fructose 1,6-bisphosphatase deficiency;
- Glucose-6-phosphatase deficiency;
- GRACILE syndrome;
- Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes;
- Pyruvate dehydrogenase deficiency;
- Pyruvate carboxylase deficiency;

- Drugs

- Linezolid;
- Phenformin;
- Metformin;
- Isoniazid toxicity;
- Propofol;
- Propylene glycol (D-lactic acidosis);
- Nucleoside reverse transcriptase inhibitors;
- Abacavir/dolutegravir/lamivudine;
- Emtricitaine/tenofovir;

- Potassium cyanide (cyanide poisoning);
- Fialuridine
- Other
 - Impaired delivery of oxygen to cells in the tissues (e.g., from impaired blood flow – hypoperfusion);
 - Bleeding;
 - Polymyositis;
 - Ethanol toxicity;
 - Sepsis;
 - Schok;
 - Advanced liver disease;
 - Diabetic ketoacidosis;
 - Excessive exercise (overtraining)
 - Regional hypoperfusion (e.g., bowel ischemia or marked cellulitis);
 - Cancers such as Non-Hodgkin`s and Burkitt lymphomas
 - Pheochromocytoma

Example 3 – Physical restitution of healthy persons after alcohol consumption

We have found that the compositions of the present invention reduce the amount or concentration or time with the presence of lactate above normal level (Total lactate load over the time) of lactate in the blood of healthy persons. This is a universal and general effect, i.e. the level of lactate will be reduces either the subject has a disease with a high level of lactate or is a healthy person where the level of lactate are higher than normal. The test persons in the example below have consumed alcohol in order to obtain a high level of lactate in the blood. We anticipate that high levels of lactate can be reduced with the composition of the present invention independent of the cause of the high level. The composition of the invention will also inhibit an increase in the lactate level since it has a general lactate reducing effect. The composition can thus be used as a preventive measure to impede high lactate levels.

Consumption of alcohol leads to elevated levels of lactate in healthy persons. The condition with lactate above 2.0 mmol/L is called hyperlactatemia and is potentially life-treating. The death from alcohol overdose is associated with extremely high lactate levels and lactate load over the time. Today

it is no effective and tailored treatment to eliminate lactate among the pharmacological medicinal tools.

Tests were performed to learn more about the features under the alcohol intake related to lactate levels in capillary blood.

- 5 **Test 1: Determination of the best site for blood taking.** Male volunteer, 49 years old consumed single dose of 250 ml red wine (13.5 %) corresponding to 33.8 g alcohol, and lactate measurements were undertaken 10 min before and during 70 min post alcohol intake. Measurements were taken in left hand and left foot.

- 10 **Test 2: Exploratory measurements of the capillary lactate in a full-scale test.** Male volunteer, 49 years old consumed totally 500 ml red wine (13,5%) corresponding to 67,5 g alcohol. Capillary lactate was measured 10 min before consumption and for 25 hours post consumption. Left foot (hallux) and left hand (fingertips) were the site for blood taking. Treatment with two portions of active drinkable was taken 645 and 910 min after alcohol intake, corresponding to 265 min interval.

- 15 **Test 3: Pilot test of full-scale test in one volunteer.** The test had been performed as described for full-scale (Test 4). This was a pilot-test on 49 years old volunteer male. During this test, the drinkable of 250 ml had been given for 2 times with 295 minutes interval. This was done with explorative objective to see the effect of two consecutive doses on reducing of lactate levels.

Design of experiment (Test 4)

- 20 Full scale experiment was performed with an objective to demonstrate therapeutic effect of the drinkable, which is a composition containing occurring soluble oxalates. The composition used also contains carbohydrates. The test on two consecutive doses of drinkable was not possible to perform because of time-schedule for participants.

- 25 **Test 4: Full-scale test on therapeutic effect of single doses of drinkable day after intake of alcohol and lactate levels.** Seven healthy volunteers had been taken individual amount of alcohol during different social event. Lactate levels were measured approx. 3 hours from the start of alcohol intake or approx. 720 min before consumption of the 250 ml drinkable. Further measurements were taken with randomly chosen intervals and near to the expected time and duration of therapeutic effect and were
30 the same for all persons.

Participants

Randomly chosen volunteers of both genders spent social evening together and consumed individual amounts of alcohol. Light food was served aside – pizza, potato chips and peanuts. Soft drinks such as Pepsi Max and Sprite were used for drink mixing. Mean age was 38 ± 12 , in the range of 22 to 49 years for whole group, where 2 of 7 were women.

Treatment in test 2-4

Soluble oxalates from naturally sources (fruits, greens, nuts and berries) were given in form of drinkable (as described in example 1) at time “0” and approx.. 720 min after the start of alcohol intake. It is important to underlay that soluble oxalates should be always used in combination with sufficient amount of sugar (carbohydrates). In example 1 (Table 1) the results of chemical composition of drinkable is reported as mean value 10 of 160 liters. The analyses were performed at German Institute of Food Technology. Amount of soluble oxalates per 250 ml drinkable was 152.5 – 177.5 mg and to this amount not less than 24.6 g carbohydrates of different kinds should be used. However, one of 6 persons with ME/CFS/SEID demonstrated better performance on lowered dose of oxalates in Placebo-test (P7).

The drinkable used here contained 152.5 mg soluble oxalates and 24.6 g of carbohydrates and was consumed by participants as fast as possible to imitate the bolus dose.

Analytical tools

Lactate levels are measured by mobile tester Lactate Scout+ from EKF Diagnostics (Germany) for self-monitoring. Fingertip or hallux was cleaned, dried and punctured by Microlet lancett fra Bayer (Germany) and 0.2 µl whole capillary blood was absorbed into Lactate Scout Sensors from SensLab GmbH (Germany). Results were manually registered in electronic format, with additional confirmation by screenshots of the monitor by iPhone-6S. Analytical reproducibility and repeatability of the lactate measurements were determined to be 2.8 % and 3.9% for 10 consecutive measurements at same day or 7 consecutive days.

Schedule for testing of lactate

In Test 1 and 2 the lactate levels were measured in both: left hand (fingertips) and left foot (hallux), while in Test 3 and 4 only measurements in left foot (hallux) were undertaken.

To avoid some unknown cycle of lactate circulation in a body, the time points were chosen randomly for first participant, and then were applied for the rest of the group. The series of 3 measurement were undertaken, because we knew that lactate levels fluctuates between the normal range of 0.5 to 2.0 mmol/L in healthy persons.

5

Results

Exploratory tests

Results of exploratory Test 1 and 2 are shown in Figure 8 and Figure 9, respectively. In our earlier work, described in co-pending patent application, the special pattern of lactate distribution between extremities was found in affected by ME/SEID/CGS/Chronic Hyperlactatemia patients: highest levels in left foot (hallux) and right hand (fingertips). Simultaneously, no such gradient distribution had been detected in healthy persons. Since, alcohol intake known to give condition of hyperlactatemia, it was necessarily to confirm that no gradient distribution could be found in healthy persons. Oppositely to this expectation, the difference in lactate distribution had been found during both tests: higher levels in left foot (hallux) then in left hand (fingertips) – Fig. 8 and 9. Therefore, in full-scale test only measurements in the left hallux had been undertaken.

Test 2 had demonstrated that lactate levels kept the same high level for 25 hours post alcohol intake (Figure 9). The lowering of lactate levels was observed only in association with intake of drinkable, two consecutive doses of 250 ml each and with interval of 265 min. Moreover, lactate levels were persistently higher in left hallux for whole examined time.

During Test 3 the more features had been unveiled on the duration of therapeutic effect (Figure 10). The first drinkable dose was given at 900 min and within next 10 min the level of lactate had lowered by 26 %, from 2.3 to 1.7 mmol/L. The maximum effect had been documented at 1050 min of experiment equal to 150 min post intake of drinkable. This was in compliance with earlier determined $T_{\max}$ for the same person: 9.5 % reduction in lactate levels at 102 min after intake of drinkable in a test of hyperlactatemia as result of physical challenge (Example 2, post exercise, where person was P3). Further, and as shown on Figure 10 the lactate levels increased during following 90 minutes by 52 %, from 1.0 to 2.1 mmol/L, which was in compliance of earlier determined duration of therapeutic effect in ME/SEID/CFS/Chronic hyperlactatemia patients corresponding to 4.5 - 5 hours. The second dose of 250 ml drinkable was given right after, at 1150 min. Once again, lowest level was measured 155 min later. Once again, $T_{\max}$ was in compliance for that for first dose: 150 min against 155 min.

To argument for the very low probability of that lowering of lactate documented in Test 3 occurred spontaneously, the Lactotagram from the same person shown on Fig. 1.1.4. His lactate levels use to be strictly within the normal range of 0.5 to 2.0 mmol/L. The fluctuations within this range are only of minor character. The largest lowering was documented between 10th and 15th minutes, e.g. exactly during the reading of a text in English. In this test, the reading was used as a stimulus or the cognitive challenged to provoke the fluctuations in lactate levels. This feature was documented in all 20 healthy volunteers who had taken the reading test and assumed to be associated with the consumption of energy for reading process, where lactate had been used as additional fuel for energy production. The interval from -60 to 0 min before reading mirrors the lactate levels without any extreme stimuli and evidence that no spontaneous large fluctuations (equal to 26 or 52% increase or decrease) had been depicted. Thus, it could be concluded that increase and decrease in lactate levels in this person in Test 3 rather due to treatment with drinkable than occurred spontaneously.

Full-scale test (N=3+1+1+1+1), Test 4

The number of persons performed this test simultaneously at the same social event were 3 males. Additionally, the first volunteer performed pilot test after the same scenario (Test 3); two females and one male performed the same test in association with other social events. Male, 49 years old had performed test once more time with increased amount of consumed alcohol. Altogether, this confirms that results were not connected to any other parameters, such as food consumed aside of the alcohol, alcohol type, and that therapeutic effect of drinkable on lowering of lactate levels is repeatable anywhere.

Amount of consumed alcohol, dose of soluble oxalates and body mass shown in Tab. 9. Figures 12-17 demonstrates the lactate levels during the test for respectively P1-3 and P5-7, while Fig.10 for P4 (the same as volunteer in Test 3).

Tab. 9 Information about participants and magnitude of the achieved therapeutic effect on lowering of lactate levels in capillary blood measured in left hallux. 1- therapeutic effect calculation as percent of lowering from lactate levels measured after expiration of the therapeutic effect; 2- therapeutic effect calculation as percent of achieved lowering from value measured before the consumption of soluble oxalates; *- P7 consumed least of all alcohol and therefore dose of 152.5 g soluble oxalates had prolonged duration.

	P1	P2	P3	P4	P5	P6	P7	Mean (S.D.)
consumed alcohol, g	176.5	159.0	150.0	141.3	196.0	156.2	97.5	
body mass, kg	120	113	122	106	106	77	85	
mg oxalates/g alcohol	0.86	0.96	1.02	1.08	0.78	0.98	1.56	
mg oxalates/kg body mass	1.27	1.35	1.25	1.40	1.44	1.98	1.79	
age	29	28	22	49	49	43	49	38 (12)
gender	M	M	M	M	M	F	F	
1 - therapeutic effect, %	50.1	29.2	21.0	36.8	40.2	28.0	*	34 (11)
2 - therapeutic effect, %	18.3	27.0	23.3	33.3	20.3	28.4	34.8	26 (6)
T _{max} therapeutic effect, min	125	125	125	150/155	125/255	125	125	
Duration of effect	255	255	255	240/240	255	255	515*	

The most classic graphic presentation of the features could be found on Figure 12 for P3 – 22 years old male, who consumed 150 g alcohol distributed in body mass of 122 kg and treated with 1.02 mg oxalates/g alcohol or 1.40 mg oxalates/kg body mass (Tab. 9). The lactate level of 1.76 mmol/L was determined 720 min and 2.3 mmol/L for 30 min prior to treatment (corresponding to 100% on Figure 19). The therapeutic effect appeared within 30 min post intake of drinkable and reached its maximum at 125 min post treatment, when it weakened and disappeared after total 255 min. During following 4 hours, the values of lactate remained at the same high level. Both, the duration and T_{max} were in compliance with corresponding values measured for P4 in Test 3. There was no time to perform the treatment with second dose. The personal perception and experience communicated by this participant was as followed: “Once I started to drink the drinkable, I became less dehydrated, nauseous and uncomfortable in the stomach (diarrhea). The body felt lighter and less rigid and headache disappeared within 38 min post treatment. I never before did experience such easy recovery from an alcohol consumption day after.” The same was truth in all meanings and features for the P2 and P3 (Tab. 9, Figure 13).

The overall trend and individual progress in absolute and relative values are shown on Fig. 18 and 19, and Tab. 9. The maximum reduction in lactate levels on response to treatment with single dose of 152.5 mg soluble oxalates was 34.8 % and 33.3 % in P7 and P4, respectively. The lowest reduction was documented in P1 and P5, by 18.3% and 20.3 %, respectively. Therefore, it was proper to examine if body mass, alcohol amount or dose could explain the differences.

Example 4 – Improvement of health as diminished symptoms for the list of Canadian Criteria

A representative example of the composition that has been used in the testing was given as following: during first 20 weeks, the dosage was gradually and systematically increased in accordance with the progression and perception of the patient. From week 21 all patients received equal medication as shown above. After all it was necessarily reduce the dosage of thiamine, which explains the lower dose from week 21.

From week 0 to 20 the dosage was gradually and systematically increased: 300 – 1200 mg alpha-lipoic acid; 3-12 mg thiamine; 27-81 niacin per day and riboflavin – 0-0.31 mg per week. From week 21: 1200 mg alpha-lipoic acid; 9 mg thiamine; 81 mg niacin per day and riboflavin 0.31 mg per week were used for self-treatment. Daily dose of oxalates in Active drinkable was as described in Example 1, 610-710 mg and was the same though all reported period.

Table shows some of the results obtained – reduced number of symptoms within given time with treatment.

Table . 10. Results of the treatment during given time on reduction of symptoms from the List of Canadian Criteria for P1, P2 and P3.

	Patient 1		Patient 2		Patient 3	
Weeks with the treatment	0	48	0	65	0	91
1. Fatigue	X	-	X	-	X	-
2.Exertional malaise						
a) Abnormal loss of physical and mental endurance . Rapid muscular and mental/cognitive fatigability . Malaise and fatigue or/and pain after load, and abnormal long recovery .	X	-	X	+/-	X	-
b) Post exertional malaise or fatigue	X	-	X	-	X	-
c) Post exertional disease worsening	X	-	X	-	X	-
3. Sleep disturbances (Table 1-2)	X	-	X	x	X	-
4. Pain	X	-	X	x	X	-
5. Neurological or cognitive symptoms						

a) Impaired short-term memory and concentration	X	-	X	X	X	-
b) Difficulty in processing information, finding words and periodically speech problems	X	-	X	X	X	-
c) Disorientation and confusion	X	-	X	-	X	-
d) Difficulty in finding words	X	-	X	X	X	-
e) Muscle weakness and muscle twitching	X	-	X	-	X	-
f) Dizziness and balance problems	X	-	X	-	X	-
g) Sensory disturbances, difficulty focusing vision , numbness / coldness	X	-	X	-	X	-
h) Hypersensitivity to light, sound and stress, which can lead to a crash periods and or anxiety	X	-	X	+/-	X	-
6A. Autonomous symptoms						
a) Orthostatic intolerance	X	-	X	-	X	-
b) Palpitations (tachycardia)	X	-	X	-	X	-
c) Irritable Bowle Syndrome, IBS	X	-	X	-	X	X
d) Difficulty breathing	X	-	X	-	X	-
e) Frequent nocturnal urination	X	-	X	-	X	-

6B. Neuroendocrine symptoms						
a) Altered temperature regulation/night sweats	X	-	X	-	X	-
b) Heat/cold intolerance	X	-	X	-	X	X
c) Anorexia or abnormal appetite	X	-	X	-	X	-
6C. Immunological symptoms						
a) Tender lymph nodes on the neck/under arm holes	X	-	X	-	X	-
b) Periodically sore throat	X	-	X	-	X	-
c) Flu-like symptoms and malaise	X	-	X	X	X	-
d) Development of new allergic reactions	X	-	X	-	X	-
e) Hypersensitivity for medicine and/or chemicals	X	-	X	-	X	-
7. Symptom stream						
a) Condition lasted for at least 6 months	X	X	X	X	X	X

b) Fatigue started with well defined debut within few weeks	X	-	-	-	-	-
c) Fatigue developed gradually	X	X	X	X	X	X
d) Fatigue and symptoms are stable or improving	X	X	-	X	-	X
e) Fatigue and symptoms are gradually worsened	X	-	X	-	X	-

We have also conducted the same experiment as described above, but without Using Active drinkable, and the results show no effect. The same was also documented by WAIS-IV test (Example 6). We can thus conclude that oxalic acid is one of the central and essential compounds of the treatment composition and achievement of the results shown in Tab. 10 is impossible without it.

Example 5 - Monitoring of health improvement during the course of self-treatment of CFS/ME/SEID with the help of lactate measurements

Effect of bolus – case A

Reading test (Lactatogram for 155 min) was taken as previously described: before treatment (Figure 22). Person (P8) arrived the test in a car as driver both times, what was against the instructions. Whatever it is the stimuli of driving or severe ME condition had caused extremely high basal levels of lactate will remain unveiled. In comparison, no such increase was detected in any of 20 healthy persons attended the test by own car (described elsewhere). This means that healthy persons regulate lactate levels within the normal range: either cognitive effort (driving, reading) or eating do not lead to increase.

Extremely high absolute values before and under the reading test appeared on Lactatogram of P8 (Figure 22). Pain in the head, foggy brain and pressure into the head, was the most profound symptoms at that point of time. To unveil the immediate effect of drinkable oxalates on reducing lactate levels, P8 was offered the consumption of 250 ml active drinkable on 10th minute post fulfilled reading. P8 reported improvement in condition and vanishing of all named symptoms within 10 minutes post intake, simultaneously as basal lactate levels dropped from 6.2 to 0.5 mmol/L. The low lactate levels remained within normal range during following 70 minutes of the test (except for one measurement at 65 min post reading).

Increased levels of lactate as result of stopped treatment at week 120 – case B

Basal levels of lactate were measured during three days before treatment was totally stopped, and measurements performed on day 1, 6 and 7 without the treatment, and on day 1 and 2 after restoration of a treatment. All measurements were performed at the same time-points ± 5 min, randomly chosen first day of experiment. Daily activity was kept identical within all four initial days and can be associated with activity at week 120.

Absolute lactate levels in capillary blood were within the normal range of 0.5 to 2.0 mmol/L, for 43 consecutive measurements during 72 hours prior to treatment stop, except for 1 value above – 2.3 mmol/L at 2377 min (Figure 23). The range for the measurements on treatment was 0.8 - 2.3 mmol/L, and raised to 1.0 - 3.0 mmol/L during first day without a treatment, and to 1.2 - 7.1 mmol/L during totally 7 days without treatment. Those values are far higher than normal range (described elsewhere). Absence of a treatment caused severe worsening of the health condition: during 7 days P1 became bed-bound with dramatically extended scope and severity of symptoms (§2) occurred simultaneously. P1 was not able to leave the bed for urination, had to be feed. Lactate levels get lower almost immediately after the treatment with full dose was re-established (Figure 23), with the range of 1.2 – 3.5 mmol/L. Improvements, such as, decrease in symptoms burden, pain relief and decreased fatigue came along with the depicted lowering of the lactate levels.

Conclusion: Based on the observations in Case A and B, the association between clinical picture, symptoms scope and severity and measured levels of capillary lactate had been established. The Lactatograms and point measurements in extremities will be further used as one of the parameters in monitoring of health improvement during self-treatment course.

Decrease in Total Lactate Load, Absolute Lactate values, Lactate in Extremities and Standard deviations as a result of self-treatment (N=6)

Lactatograms were taken as described elsewhere: before start and at 20 weeks of treatment. Point measurements in extremities had been performed at the same time as Lactatograms. Validation of the Lactatograms was performed on three parameters: (1) Absolute values of Lactate in capillary blood; (2) Total Lactate Load measured as AUC_{155} ; (3) Standard deviation in full set of 26 measurements. Measurements in extremities were validated on three parameters: (1) Absolute values in each

extremity; (2) Mean of all 4 measurements (right foot, left foot, right hand and left hand); (3) Standard deviation for 4 measurements.

Absolute values of lactate correspond to the real-time fluctuations of lactate and should be compared with normal range, which is 0.5 – 2.0 mmol/L. Total Lactate Load gives a picture of lactate fluctuations and levels during consecutive 155 min and reflect the symptom related experience and perception of person's own health form under the test. Since standard deviation describes variety within a data set, the size of it gives association of how unpleasant person felt during 155 min of monitoring. All mentioned above parameters thought to correspond to the fast-circulating and/or newly produced lactate, in same manner as glucose measurements used in diabetics. In contrary, overload of lactate was found in lower extremities as described elsewhere, away from important organs such as heart and brain. Therefore, measurements in extremities give a picture of lasting lactate or lactate load over the time, in the same manner as HbA_{1c} used in monitoring of the diabetics.

Six of eleven persons were tested: P1, P3, P7, P8, P11 and P12. Two of eleven had terminated treatment or did not want to be measured (P5, P6). Three of eleven started treatment long before test was developed and therefore were not measured at all (P2) or some parameters are missing (P1, P3). One of eleven persons had severe condition and could not be tested yet (P4). One of eleven persons did not come to 20 weeks yet (P9).

Four parameters were calculated from 26 points on Lactatogram and 4 measurements in extremities. Improvement of the 4 of 4 measured parameters in P8 shown on Fig. 22 and where in compliance with each other - Absolute Values and Total Lactate Load (AUC_{155}), both decreased by 64-67%. Decreased Standard deviations for both mentioned parameters were in compliance with reported health improvement during 20 weeks (Tab. 21), as decrease in symptom number from 21 to 11 and increase of CEDL from 10.6 to 30.6 (Tab. 22). Lowered mean value of lactate in extremities (lasting lactate in the body) was also reduced in the same magnitude – by 64%, reflecting the persistent effect of the treatment on lowering of lactate load over the time.

Decrease by same magnitude of 35% was documented for all parameters in P7 - Absolute Value of capillary lactate, Total Lactate Load, Lactate in extremities, along with decreased values of standard deviations for all parameters (Table 16), simultaneously as number of symptoms decreased from 21 to 15 (Tab.21) during 20 weeks of treatment. CEDL validation was compromised by change to walk by own force instead of using walking chair (Tab.22).

Decrease by 15% was detected in P11 in Lactate in Extremities, corresponding to reduction of lactate load over the time. Lactate values were in good compliance with reported lowering of symptom number from 22 to 16 (Table 21) and increase of CEDL from 0.80 to 1.03 (Table 22) during 20 weeks of treatment. Unexpected increases in Total Lactate Load and mean of Absolute capillary values were documented in P11, as only one of six measured persons, and was 16%. For instance, analytical day-to-day variation of the test apparatus was calculated to be 3.8 % for 7 consecutive days and thus, cannot explain this increase alone. However, the person itself explain the difference by unusually good form on a test day before the treatment.

10 Decrease in P3 by 45% was documented for Lactate in Extremities.

The reduction of 47% for Lactate in Extremities for P12 coincidence with increased of the CEDL from 3.99 to 7.26 during 20 weeks of treatment (Table 22). It might have indicated that values of lasting lactate have some association to fatigue and stamina perception and experience. The modest reduction of 8% in Total Lactate Load coincidence to absence of reduction in symptom number during those 20 weeks (Table 21): 10 and 11 reported symptoms left at both time points. On another hand, the decrease in mean of Absolute capillary values and Standard deviations of all parameters, might evidence for less variation in measured values and more pleasant daily experience.

20 The special attention should be draw to parameter such as Lactate in Extremities, because this value mirrors the lasting lactate levels in the body and associated with defense mechanism of the body to drain the excess of lactate away from heart, brain and other organs. In the same manner as HbA_{1c} mirrors the lasting over the time levels of glucose. The value of lasting lactate had decreased in all measured persons (Table 16). The meaning of it could be explained as permanent decreased production or increased clearance of lactate in the body as response to the treatment with among others drinkable oxalates. All measurements were in compliance with the reported decrease in symptoms burden (Figure 24) and fatigue presence (Figure 25) and increased daily activity – CEDL (Tab. 22).

30

Table 16. Parameters from lactatograms before and under the treatment and under the placebo-test.

	Capillary Lactate, mmol/L (+/- S.D.), N=26			Total Lactate Load, mmol/L*min, (AUC ₁₅₅)			Mean Lactate Level in Extremities, N=4		
	Before Treatment	20 weeks with treatment	7-18 days after exchange	Before Treatment	20 weeks with treatment	Placebo test	Before Treatment	20 weeks with treatment	7-18 days after exchange
User 1	3.0 (1.0)	1.92 (0.4)	2.20 (0.8)	464.8	303.0	351.8	8.4 (7.6)	n.d.	n.d.
User 3	n.d.	n.d.	1.80 (0.8)	n.d.	n.d.	268.0	n.d.	1.7 (0.4)	3.9 (3.1)
User 7	3.5 (1.8)	2.24 (0.9)	2.25 (0.9)	537.7	345.0	344.0	5.3 (4.1)	1.8 (0.4)	2.3 (1.8)
User 8	3.5 (3.2)	1.25(0.4)	1.44 (0.5)	571.9	188.7	231.9	1.7 (0.6)	1.1 (0.5)	1.5 (0.1)
User 11	1.8 (0.8)	2.1 (0.6)	2.1 (0.6)	268.2	311.2	325.2	2.3 (0.4)	2.0 (0.8)	2.0 (0.8)
User 12	1.8 (1.1)	1.8 (0.4)	1.6 (0.4)	298.3	274.5	245.0	3.9 (2.7)	2.1 (0.5)	1.8 (0.7)

5

Example 6 – Cognitive restitution under the treatment for CFS/ME/SEID and HyperlactatemiaIntroduction

The background for testing cognitive functioning was an interest from the subject herself. She had recently been diagnosed with a condition Myalgic Encephalomyelitis (ME). She was already suffering from variety of the somatic symptoms (described above), when experienced the dramatic reduction in her cognitive abilities. The extremely and most dramatic worsening came fast; only within a few weeks she lost her ability to function normally on the daily basis. This reduction was of such degree and scope that she could not understand the 1-3 steps instructions for making a bag soup; loss ability to understand the foreign language she used on daily basis at work (English); could not find the words in her operative daily language (Norwegian); the logical practical operations such as order of operations during “pour a cap of a tea from the machine” was disrupted and reasoning of the order took extremely long time (some few seconds longer than she was used to). Moreover, she could not understand the words spoken to her and used few minutes to understand short sentences; was not able to perform the mathematical operations such addition and subtraction, the multiplication was forgotten for good. She could not perceive the spoken two-digits numbers. It seems that all cognitive operations took longer time than she was used to. All this together made her afraid of her health condition and cognitive functioning.

Unfortunately, the cognitive dysfunction is usual for whole group of the ME/SEID/CFS/Chronic hyperlactatemia affected patients and some of the mentioned above symptoms are on the List of the Canadian Criteria (2003), which is necessarily to fulfil to get the diagnosis (elsewhere).

The hypothesis was as following: The novel mix of niacin-riboflavin-thiamine-alpha-lipoic acid alone or in combination with drinkable mix of oxalates and carbohydrates can have a positive effect on cognitive functioning in persons affected by ME/SEID/CFS/Chronic hyperlactatemia.

5

Methods

At the assessment time the subject was 45 years old, she was on the sick leave from her work as a leader and researcher. On the other hand, she was optimistic due to possibility of recovering. CDL-90 test was performed before WAIS-IV test to exclude the depression or other psychological disorders.

10 This test was negative on any disorders and it was decided to perform WAIS-IV test.

The subject was tested with WAIS-IV three times. First time full scale, and second and third time partially with subtests inside the working memory index and process speed index. The authorised phycologist performed the tests in his office.

15 The subject was aware of that energy level can affect the outcome of the tests and minimised the potential variations by doing the same routines at least for 3 days prior to testing, by keeping the same number of steps per day, scope of activities and their duration and nutritional diet before each assessment.

The subject, who was the same as P1 in rapport on self-treatment for ME/CFS/SEID/Chronic hyperlactatemia, was tested 3 times:

- 20
1. *Assessment: Full scale WAIS-IV, date 28.08.2014;*
 2. *Assessment: Partial WAIS-IV, date 30.09.2014;*
 3. *Assessment: Partial WAIS-IV, date 05.12.2014.*

Following treatment was used at corresponding assessments:

- 25
- a) 28.08.2014 corresponds to period without treatment;
 - b) 30.09.2014 corresponds to day 26 in a 33 days-long period with treatment by alpha-lipoic acid 300 mg once a day. Alpha-lipoic acid was taken 10:57 a.m. – right before the test started at 11:00 a.m. Additionally 250 ml of drinkable had
- 30
- been taken together with food at 10:42 a.m. This was a not routine, but at that time she used drinkable occasionally without understanding how to use it or why to use it. This was an exploratory and intuitive way to use it – on the demand of the body, with only signal – flu-like feeling and freezing.

- c) 05.12.2014 corresponds to result from 66 days with steadily increased dose of ALA, where last 29 days were with treatment by 1200 mg alpha-lipoic acid + 12 mg thiamine + 27 mg niacin + 2.5 mg riboflavin per day in addition to two portions of drinkable, 250 ml each per day. On the test day 300 mg Alpha-lipoic acid was taken at 10:57 a.m., but the subject forgot to take the drinkable at 10:42 a.m. together with food as she did last time (assessment on 30.09.2014).

RESULTS

Assessment before treatment start – ME/CFS/SEID/Chronic Hyperlactatemia – 28.08.2014

Scores on the indexes shows functioning above average on all indexes. The full-scale score is not valid because of the huge discrepancy in scores between the indexes.

VCI = IQ 139, (99,5%)

PRI = IQ 126, (96%)

WMI = IQ 105, (63%)

FPSI = IQ = 112, (79%)

PSIQ = 126, (96%)

GAI = 138 (99%)

In this score, we have to use the General Ability Index (GAI) which is very high and based on Verbal Comprehension (VCI) and Perceptual reasoning (PRI). Since the score on Working memory (WMI) and Process speed (PSI) is a lot lower than the others, it is reasonable to assume that the subjects experience of lower functioning than her normal state, is reflected in the scores on those two indexes. The discrepancy between index scores that makes it also reasonable to assume that the FSIQ would have been higher in her normal state, and that GAI best reflects her intellectual capacities without illness.

Assessment: Partial WAIS-IV, date 30.09.2014

The test was performed on 26th day with 300 mg/day of Alpha-lipoic acid (ALA). The 300 mg ALA, 153 mg soluble oxalates with 25 g carbohydrates had been taken within 18 minutes prior to the test. The second test gives a valid result on Working memory and one subtest result on PSI and two subtest results on PRI: WMI=IQ 116 (86%). The results give significant higher score in working memory, and no valid differences in scores on process speed or Perceptual reasoning.

The perception of the second test was described by the subject in her diary: “Pictures which were used in the test were not that blinding as during the first assessment. The testing professional had assured me that the same lighting was used. That could mean that I became less light sensitive during this
5 moths with the treatment. The problems with the vision was during both tests. However, it was much easier to percept the long rows of numbers, despite of it the boarder of how many numbers I could remember was very clear. I did not felt enough strength in the brain to remember all of them. Opposite to the first assessment I had strength in the brain, and not a porridge or black blanket as at first test. Despite of it, it was not enough that I could solved some mathematical assignments, simply
10 because I could not perceive two-digits numbers during all assessments...”

Assessment: Partial WAIS-IV, date 05.12.2014

The test was performed after 2 months, where last 29th days were on the treatment consisting the novel mix of 1200 mg alpha-lipoic acid + 12 mg thiamine + 27 mg niacin + 2.5 mg riboflavin per day
15 in addition to two portions of drinkable, 250 ml each. On the test day, the only 300 mg ALA had been taken within 18 minutes, while the subject forgot to take the drinkable before the test. The third assessment gives a valid result on Working memory and one subtest on PSI and two subtest results on PRI: WMI = 96 (39%). The scores give a significant loss in scores compared to first and second assessment. However, when we look in to the subtest scores, and look at the scores on the two main
20 subtests administrated under all of the three assessments, the scores are basically the same with same variation.

Discussion and Conclusion

The WAIS-IV shows that the subject has a high level of cognitive functioning, with high IQ, but a
25 significant lower functioning on the working memory index and the process speed index. These results are in accordance with her experienced symptoms and illness (ME/SEID/CFS/Chronic hyperlactatemia).

The increase of Working memory score by 23 % from 63 to 86% measured on 26th day of treatment
30 most likely due to treatment with 300 mg ALA on the long term. However, at the test day, 18 minutes prior to test the person had taken both the ALA and oxalates. General knowledge is that ALA absorbs into the blood stream within 30 min and excreted via urine within 30-60 min post intake. This is in

compliance of the time for noticeable therapeutic effect in ME/SFC/SEID patients who use our self-treatment (described elsewhere). However, ALA is both water- and fat-soluble and therefore its pharmacokinetics have to be more complicated and affected by body fat index. On another hand, soluble oxalates are only water soluble. Our numerous tests on healthy and ME affected persons had confirmed that effect is noticeable already within 10 min, with T_{max} of 102- 150 min post intake and effect duration for 4,5 – 5 hours. Therefore, it is reasonable to say that maximum effect of oxalate coincidence with the test period. Therefore, it is not possible to exclude oxalate as a potential candidate responsible for the achieved therapeutic effect.

This assumption could be also deducted from the results of the test on 05.12.2014, when treatment was extended by new compounds and increase dose of ALA from 300 to 1200 mg a day when it comes to the long-term effect of the treatment. However, at that test day the person had taken only 300 mg ALA, e.g. the same amount as at the day of the second assessment and did not taken 250 ml of drinkable with 153 mg soluble oxalates and 25 g mixture of carbohydrates. Therefore, if we were looking away from the long-term effect and assume that only treatment taken before the test would affect the outcome, then the difference lies only in absence/presence of soluble oxalates in a treatment taken before the test.

Working Memory score increased by 23% on the test day 30.09.2014, when oxalates were taken, and opposite, when oxalates where not taken, the decrease in Working Memory score by 47 % on the test 05.12.2014 were documented.

From this day, the extremely importance of the oxalates for cognitive functioning had been discovered. The treatment had been adjusted in such way that systematic supply of soluble oxalates along with carbohydrate mix was combined with systematic supply of novel formulation of alpha-lipoic acid – niacin – thiamine –riboflavin during a day.

Today, the test person is fully functioning and has none cognitive difficulties experienced before the treatment. She is able to concentrate herself for many hours, as it was before her illness. We suggest including the soluble oxalates on the list of chemical compounds with ability to improve cognitive functioning and cognitive restitution. However, we aware that test on several persons should be performed. On another hand, 11 persons affected with ME/SEID/CFS/Chronic hyperlactatemia who uses the self-treatment had reported improvement of their cognitive functioning, among other:

exertional malaise, including abnormal loss of mental endurance, rapid mental/cognitive fatigability, and abnormal long recovery; post exertional malaise or fatigue; post exertional disease worsening; impaired short-term memory and concentration; difficulty in processing information, finding words – all from the list of Canadian Criteria (2003). In addition, they also reported less severity of the cognitive symptoms associated with fatigue, such as: concentration problems; problems to think clearly; memory problems; difficulties to find the words. The reduction in symptoms and reduction of fatigue presence corresponds to the results achieved by treatment and as documented also applies to the cognitive restitution of the ME/CFS/SEID/Chronic Hyperlactatemia patients.

The next evidence of that oxalates plays a role in cognitive recovery of ME/CFS/SEID/Chronic hyperlactatemia patients would be the results from test on lowering oxalate dose (placebo-exclusion test). Fig. 25 shows fatigue presence at 20 or 110 weeks on the same treatment as described for assessment 3 in this report; three days on the same treatment, including 610 mg soluble oxalates per day along with carbohydrate mix and vitamin-ALA mix; 5 to 22 days on lowered by 60% dose of soluble oxalates, carbohydrate mix and vitamin-Ala mix; and again 5 to 22 days on 610 mg oxalates, carbohydrates and vitamin-ALA mix. Thus, amount of carbohydrates and novel formulation of ALA with vitamins were not affected by lowering oxalate dose (Tab. 1.) in the Placebo-test, they will be not discussed.

The overall trend for the 6 tested persons with ME/SEID/CFS/Chronic hyperlactatemia shown on Figure 26. There were 11 questions in the questionnaire “Fatigue Scale/Presence, FS”, where 4 of them were addressed difficulties in cognitive functioning. Minimum points on this schema was 0 and maximum 33, where 0-12 points were accounted for cognitive functioning. For example, P11 had reported mean score of 9 after 20 weeks with 610 mg oxalates/day and increased to 28 within 14 days on lower dose of 270 mg/day. The increase in score was due to corresponding increase from 4 to 8 points for cognitive functioning on 4th day and from 8 to 9 during 5th day and finally to maximum 12 points after 1 week on reduced dose of oxalates. The same was truth for 5 of 6 persons tested: the person P7 did not have any fluctuations in mentioned symptoms during this test.

On the long term, all 11 persons had reported improvement in their cognitive functioning: P3 and P4 spending now about 4 hours a day of exercising mathematics and cross-words. P8 reading a lot and able to remember better; P12 working as a teacher at 20%; P1 can work for 10 hours some days with writing; P2 and P5 reported that their thoughts became faster and clear. P9 is only in the beginning of the recovery and did not experienced much difference yet.

CONCLUSIONS

- The soluble oxalates were documented to improve the Working memory score according to WAIS-IV assessment when used in combination to alpha-lipoic acid. However, the alpha-lipoic acid alone did not have the same therapeutic effect. Therefore, the achieved effect was credited to the soluble oxalates.
- To maintain the long-term therapeutic effect on cognitive functioning, the systematic supply of at least 610 mg soluble oxalates per day should be assured in mandatory combination with carbohydrate mix and combination to optional dose of novel formulation of alpha-lipoic acid + thiamine + niacin + riboflavin per day.
- The soluble oxalates had been shown to play key-role in the cognitive recovery of the ME/CFS/SEID/Chronic Hyperlactatemia patients supplied with described above treatment on the long-term basis.
- The therapeutic effect was demonstrated to be dose-dependent and thus could not be due to placebo-effect.
- The cognitive functioning is very vulnerable to the absence of the treatment and symptoms had shown reversible nature and appears/disappears in the same order in the same person, each time treatment stops or starts.
- We claim that oxalates can be used for cognitive restitution, recovery and maintenance of normal cognitive functioning in conditions associated with hyperlactatemia or not.

Administration of the composition of the present invention

As a pharmaceutical medicament the compositions of the present invention may be administered directly to the patient or animal by any suitable technique, including parenterally, intranasally, orally, or by absorption through the skin. They can be administered locally or systemically. The specific route of administration of each agent will depend, e.g., on the medical history of the patient.

Examples of parenteral administration include subcutaneous, intramuscular, intravenous, intraarterial, and intraperitoneal administration.

For parenteral administration, in one embodiment, the compositions of the present invention are formulated generally by mixing each at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-

toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation.

For oral pharmacological compositions such carrier material as, for example, water, gelatine, gums, lactose, starches, magnesium-stearate, talc, oils, polyalkene glycol, petroleum jelly and the like may be used. Such pharmaceutical preparation may be in unit dosage form and may additionally contain other therapeutically valuable substances or conventional pharmaceutical adjuvants such as preservatives, stabilising agents, emulsifiers, buffers and the like. The pharmaceutical preparations may be in conventional liquid forms such as tablets, capsules, dragees, ampoules, drinkable solutions and the like, in conventional dosage forms.

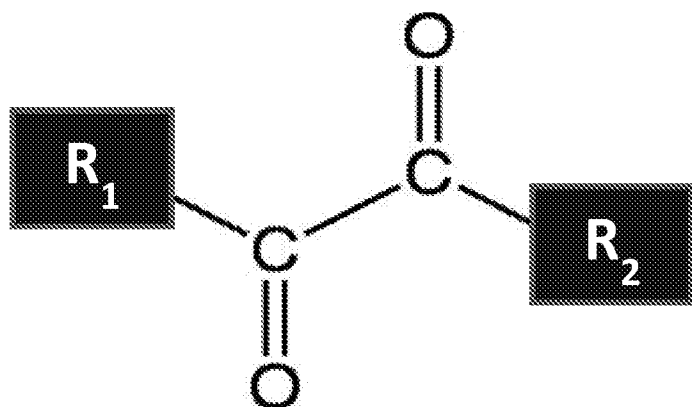
References:

1. Honow, R., & Hesse, A. (2002). Comparison of extraction methods for the determination of soluble and total oxalate in foods by HPLC-enzyme-reactor. *Food Chemistry*, 78, 511-521.
2. Al-Wahsh, I. A., Wu, Y., & Liebman, M. (2012). A Comparison of Two Extraction Methods for Food Oxalate Assessment. , Vol. 1 No. 2, 233-237.
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CLAIMS

1. A composition for the prevention and/or treatment of hyperlactataemia or lactic acidosis,
 5 wherein said composition comprises oxalate or oxalic acid, or a salt, prodrug, derivative or metabolite thereof.

2. The composition according to claim 1, wherein said composition comprises an oxalic compound of the formula



where;

$R_1=OH$ and $R_2=OH$ is oxalic acid, or

15 $R_1=H_2N$ and $R_2=ONa$ is sodium oxamate, or

$R_1=H_2N$ and $R_2=OK$ is potassium oxamate, or

$R_1=H_2N$ and $R_2=CaO$ is calcium oxamate, or

$R_1=O^-$ or $R_2=OH$ is hydrogenoxalate, or

$R_1=K^+O^-$, $R_2=OH$ is potassium hydrogenoxalate, or

20 $R_1=O^-$ and $R_2=O^-$ is oxalate, or

$R_1=NaO$ and $R_2=NaO$ is sodium oxalate, or

$R_1=CaO$ and $R_2=CaO$ is calcium oxalate

25 3. The composition according to claim 1, comprising a compound selected from the group consisting of magnesium oxalate, potassium oxalate, oxalic acid anhydrous, oxalic acid dihydrate, lithium oxalate, cesium oxalate, oxaloacetic acid, lithium oxamate, cesium oxamate, magnesium oxamate, caesium oxalate, beryllium oxalate, potassium oxalate, oxalic

acid anhydrous, oxalix acid dyhydrate, lithium oxalate, sodium oxalate, thallium (I) oxalate, uranyl oxalate, gallium oxalate, gold oxalate, magnesium oxalate, mercury (II) oxalate, manganese oxalate, nickel oxalate, barium oxalate, silver oxalte, iron (II) ferrous oxalate, scandium oxalate, cadmium oxalate, and calcium oxalate.

5

4. The composition according to claim 1, wherein the composition also comprises lipoic acid, preferably alpha-lipoic acid (ALA).

10

5. The composition according to claim 1, wherein the composition also comprises thiamine, B₁.

6. The composition according to claim 1, wherein the composition also comprises niacin, B₃.

7. The composition according to claim 1, wherein the composition also comprises Riboflavin, B₂.

15

8. The composition according to claim 1, wherein the composition also comprises a sugar.

9. The composition according to claim 8, wherein the sugar is one or more sugars selected from the group consisting of sucrose, glucose, fructose, maltose and lactose.

20

10. The composition according to any of the claims, for the prevention and/or treatment of hyperlactataemia.

25

11. The composition according to any of the claims, for the prevention and/or treatment of lactic acidosis.

30

12. The composition according to any of the preceding claims, for use in the prevention and/or treatment of chronic fatigue syndrome (CFS)/ myalgia encephalomyelitis (ME)/ systemic exertion intolerance disease (SEID) or fibromyalgia wherein hyperlactataemia is a component or symptom.

13. The composition according to claim 10, wherein the hyperlactataemia is with lactic acidosis.

35

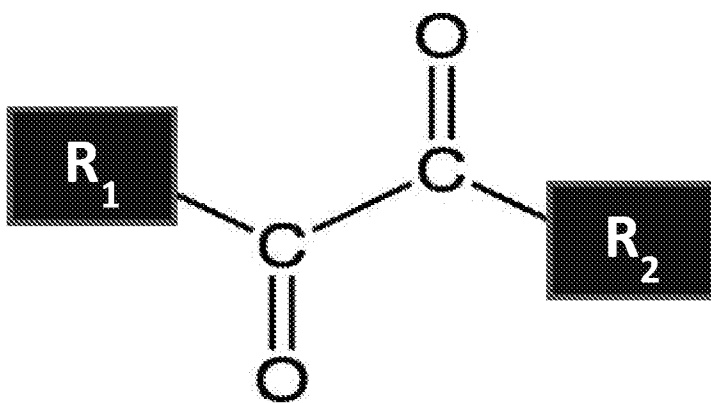
14. The composition according to claim 10, wherein thee hyperlactataemia is without lactic acidosis.

15. A pharmaceutical or nutritional composition for reducing the amount of lactate in the blood of an animal, comprising administering said composition to a patient in need thereof, and wherein said composition comprises oxalate or oxalic acid, or a salt, prodrug, derivative or metabolite thereof.

5

16. The composition according to claim 15, wherein said composition comprises an oxalic compound of the formula

10



where;

$R_1=OH$ and $R_2=OH$ is oxalic acid, or

15 $R_1=H_2N$ and $R_2=ONa$ is sodium oxamate, or

$R_1=H_2N$ and $R_2=OK$ is potassium oxamate, or

$R_1=H_2N$ and $R_2=CaO$ is calcium oxamate, or

$R_1=O^-$ or $R_2=OH$ is hydrogenoxalate, or

$R_1=K^+O^-$, $R_2=OH$ is potassium hydrogenoxalate, or

20 $R_1=O^-$ and $R_2=O^-$ is oxalate, or

$R_1=NaO$ and $R_2=NaO$ is sodium oxalate, or

$R_1=CaO$ and $R_2=CaO$ is calcium oxalate

25 17. The composition according to claim 15, comprising a compound selected from the group consisting of magnesium oxalate, potassium oxalate, oxalic acid anhydrous, oxalic acid dihydrate, lithium oxalate, cesium oxalate, oxaloacetic acid, lithium oxamate, cesium oxamate, and magnesium oxamate.

18. The composition according to claim 15, wherein the composition also comprises lipoic acid, preferably alpha-lipoic acid (ALA).
- 5 19. The composition according to claim 15, wherein the composition also comprises thiamine, B₁.
20. The composition according to claim 15, wherein the composition also comprises niacin, B₃.
21. The composition according to claim 15, wherein the composition also comprises Riboflavin,
10 B₂.
22. The composition according to claim 15, wherein the composition also comprises a sugar.
23. The composition according to claim 8, wherein the sugar is one or more sugars selected from
15 the group consisting of sucrose, glucose, fructose, maltose and lactose.
24. The composition according to any of the claims 15-23, for the prevention and/or treatment of
hyperlactataemia.
20
25. The composition according to any of the claims 15-24, for the prevention and/or treatment of
lactic acidosis.
26. The composition according to any of the preceding claims 15-25, for use in the prevention
25 and/or treatment of chronic fatigue syndrome (CFS)/ myalgia encephalomyelitis (ME)/ systemic
exertion intolerance disease (SEID) or fibromyalgia wherein hyperlactataemia is a component or
symptom.
27. The composition according to claim 15, wherein the Total Lactate Load or the amount of
30 lactate in the blood is reduced in an animal having a higher amount of lactate than normal.
28. The composition according to claim 15, wherein the higher amount of lactate is a
consequence of physical training or exercise.

29. The composition according to claim 15, wherein the higher amount of lactate is a consequence of intake of alcohol.

30. The composition according to claim 15, wherein the higher amount of lactate is an effect of a disease.

31. The composition according to claim 15, wherein the reduction of lactate is for treatment or prevention of conditions selected from the group consisting of Biotinidase deficiency, multiple carboxylase deficiency, or nongenetic deficiencies of biotin; Diabetes mellitus and deafness; Fructose 1,6-bisphosphatase deficiency; Glucose-6-phosphatase deficiency; GRACILE syndrome; Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; Pyruvate dehydrogenase deficiency; Pyruvate carboxylase deficiency; Impaired delivery of oxygen to cells in the tissues (e.g., from impaired blood flow – hypoperfusion); Bleeding; Polymyositis; Ethanol toxicity; Sepsis; Shock; Advanced liver disease; Diabetic ketoacidosis; Excessive exercise (overtraining); Regional hypoperfusion (e.g., bowel ischemia or marked cellulitis); Cancers such as Non-Hodgkin's and Burkitt lymphomas and Pheochromocytoma or for use of medicaments selected from the group consisting of Linezolid; Phenformin; Metformin; Isoniazid toxicity; Propofol; Propylene glycol (D-lactic acidosis); Nucleoside reverse transcriptase inhibitors; Abacavir/dolutegravir/lamivudine; Emtricitabine/tenofovir; Potassium cyanide (cyanide poisoning); and Fialuridine.

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Figure 1

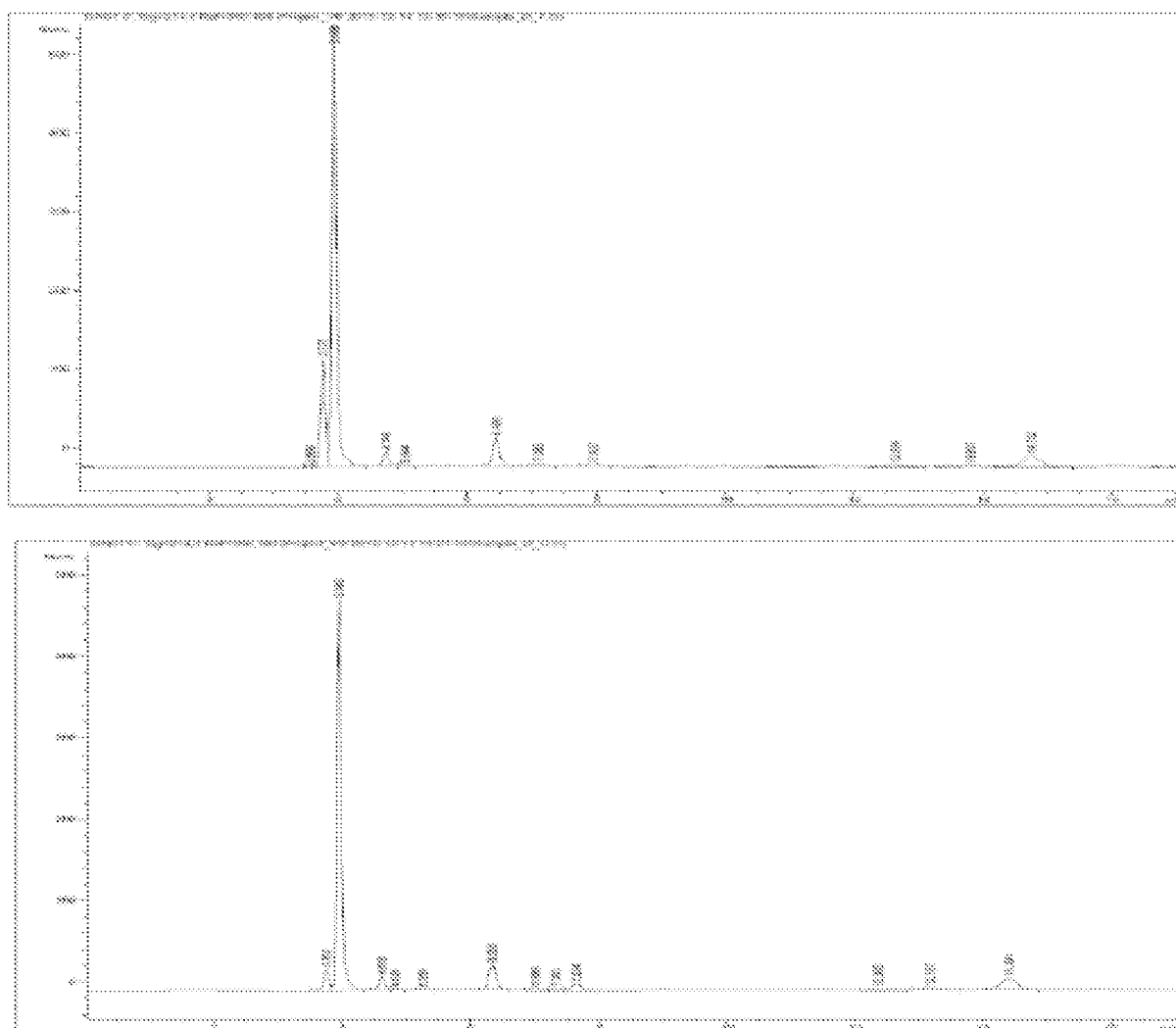
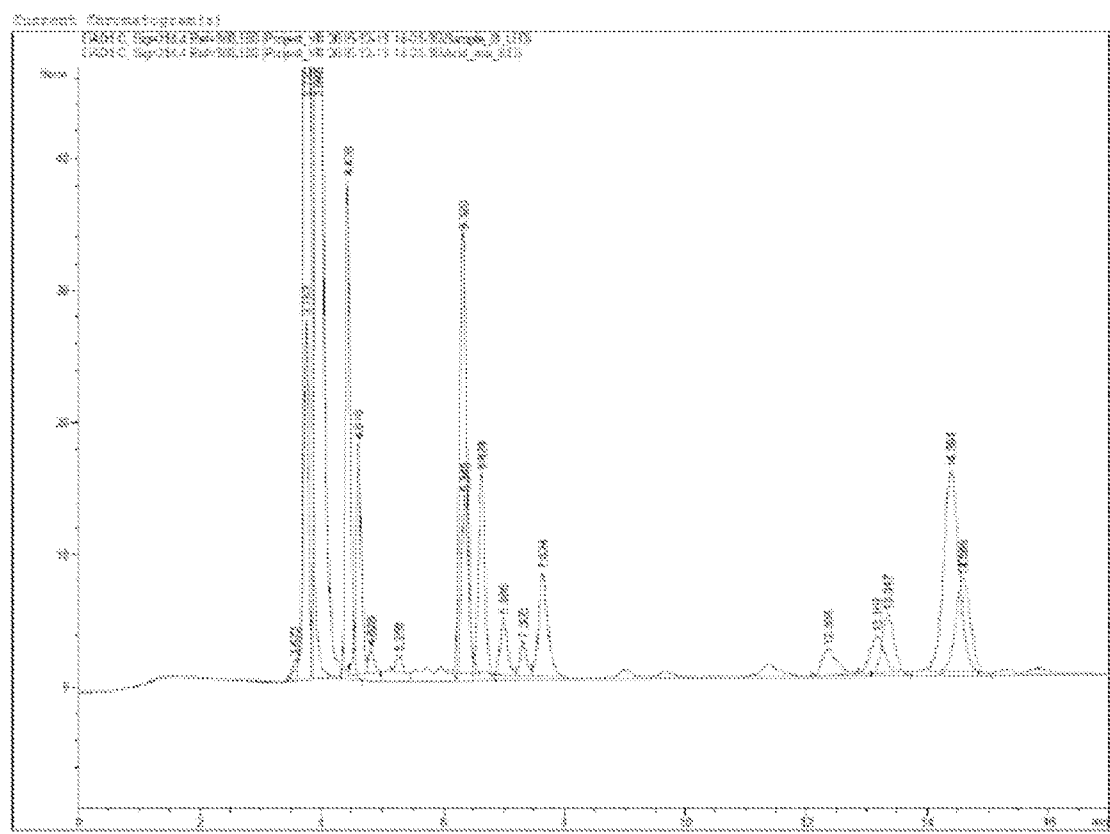


Figure 2



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Figure 3



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Figure 4

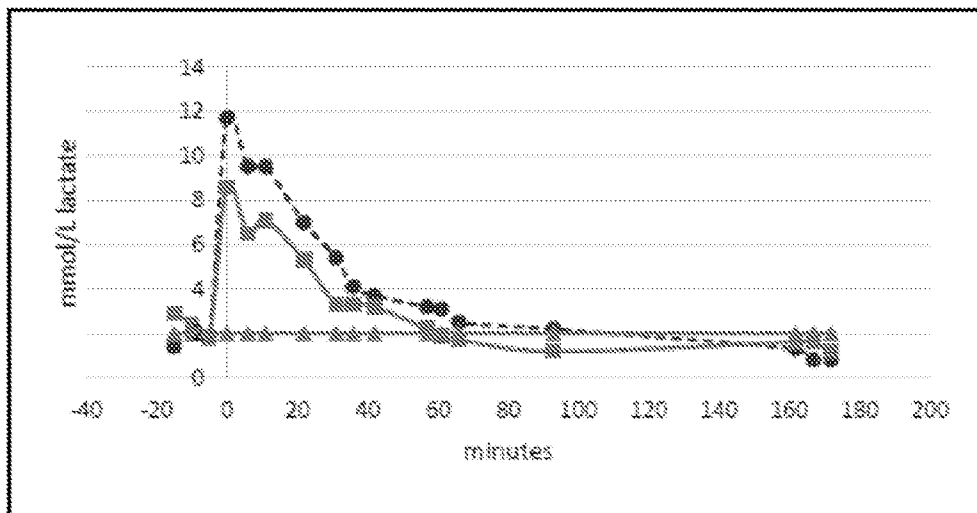
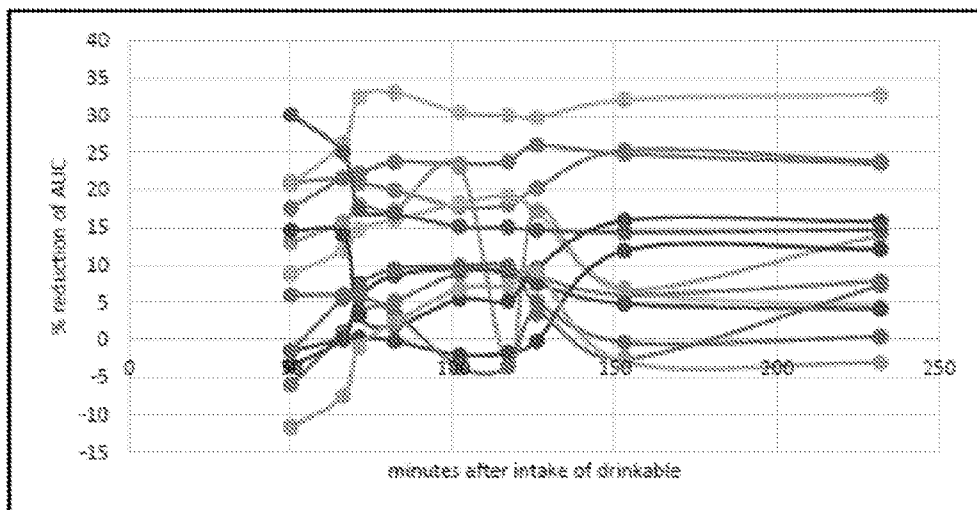


Figure 5



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Figure 6

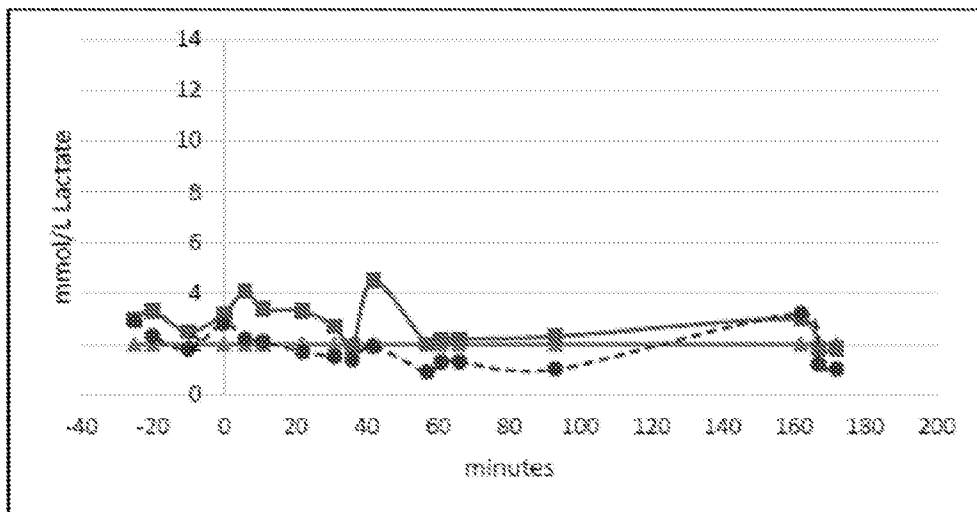
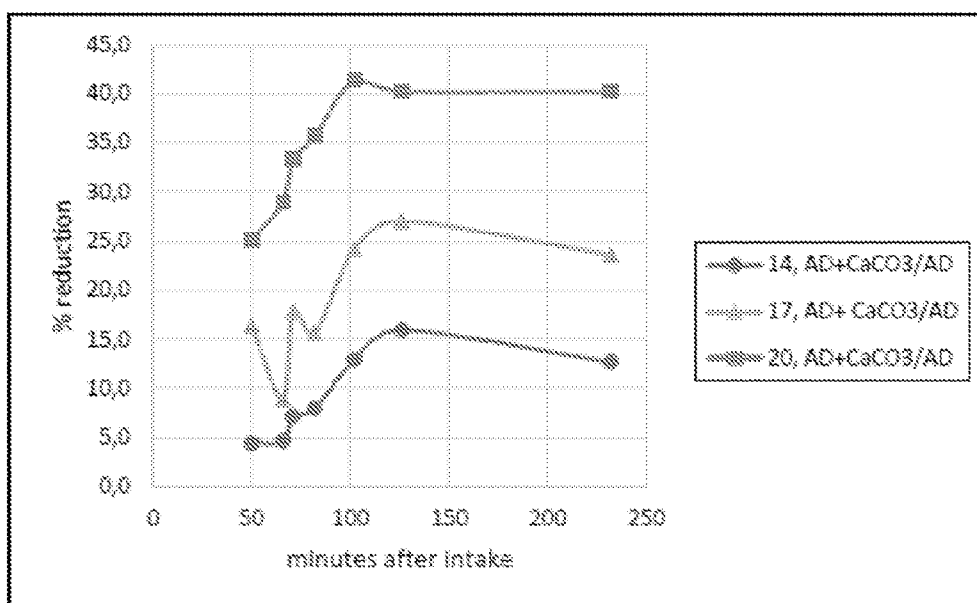


Figure 7



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Figure 8

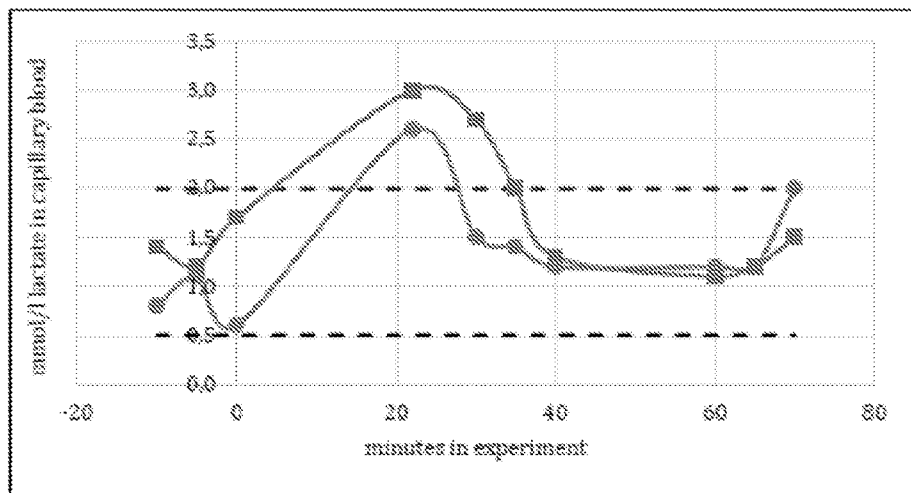
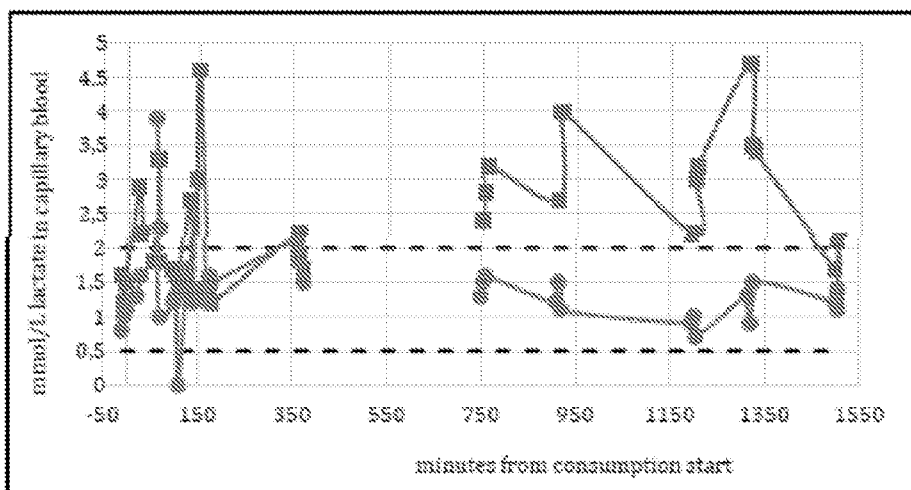


Figure 9



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Figure 10

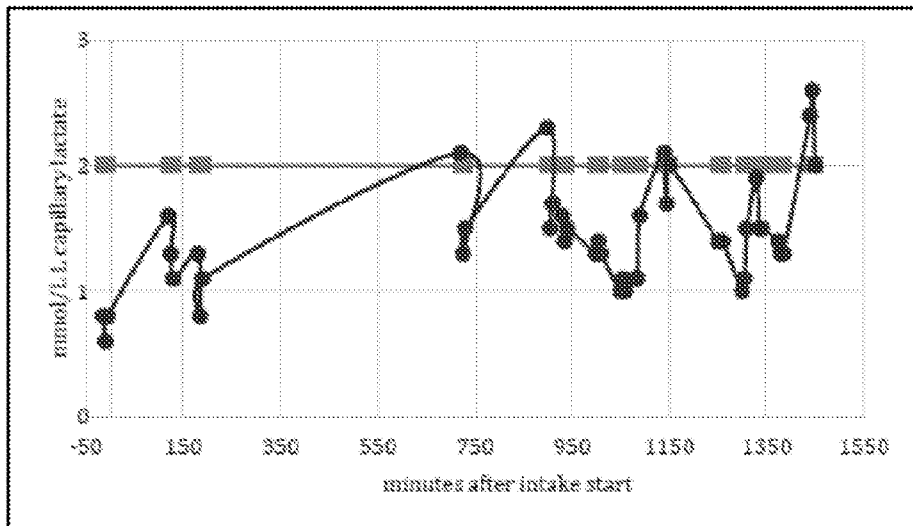
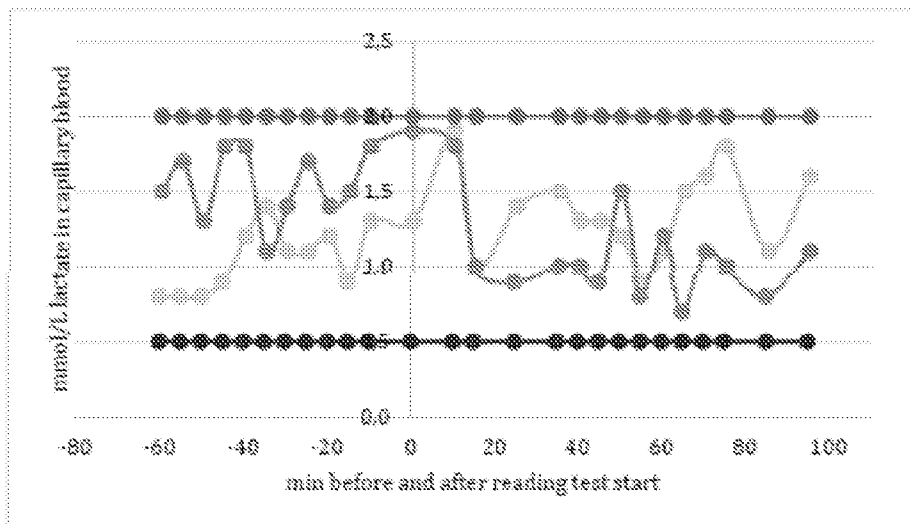


Figure 11



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Figure 12

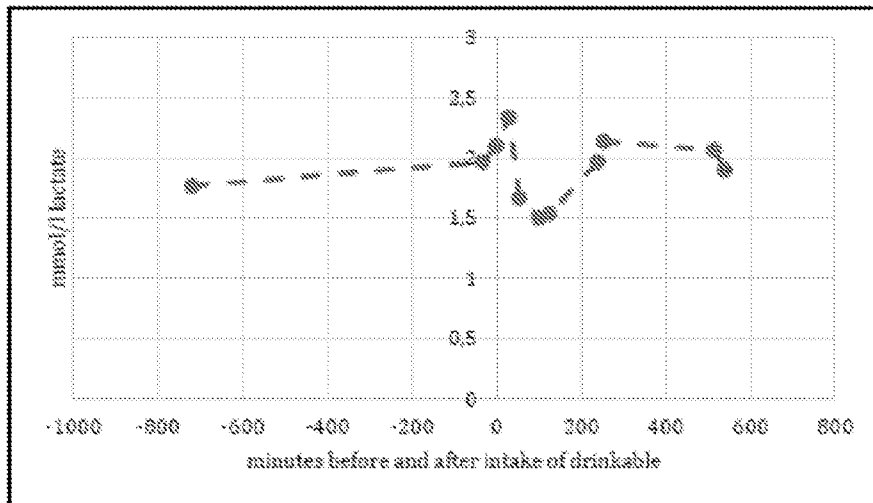
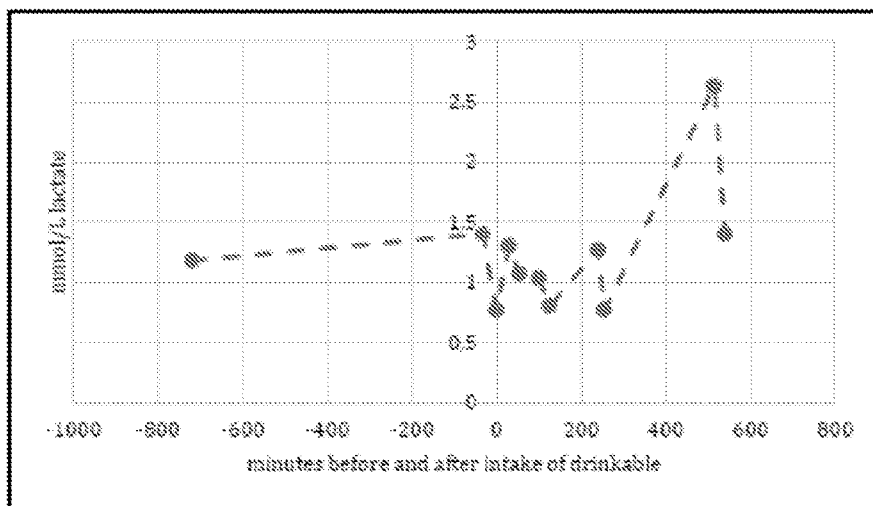


Figure 13



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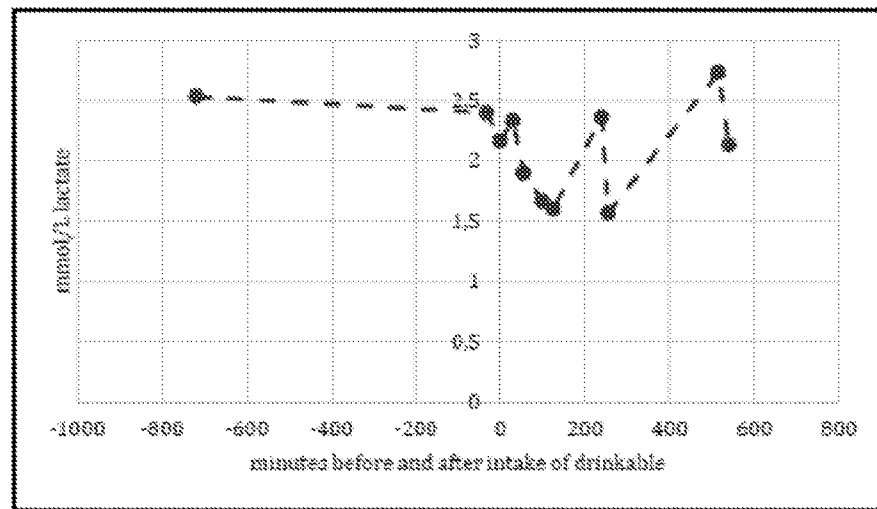


Figure 14

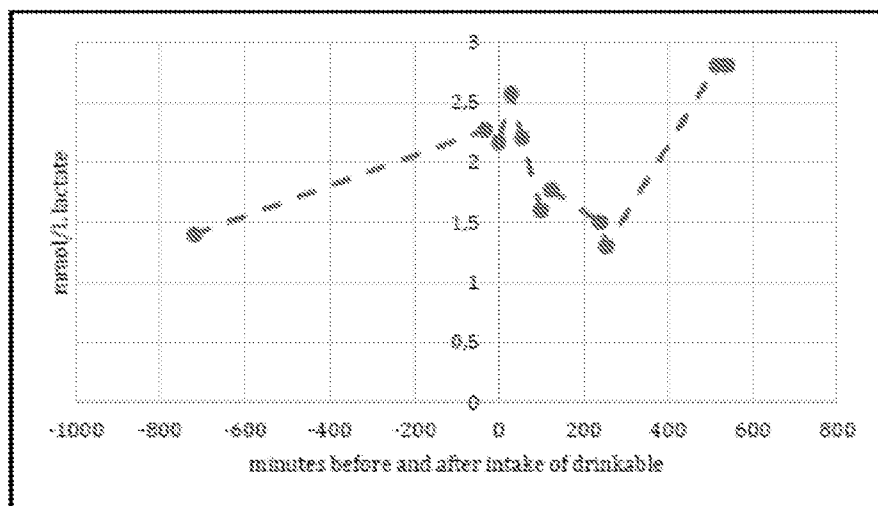


Figure 15

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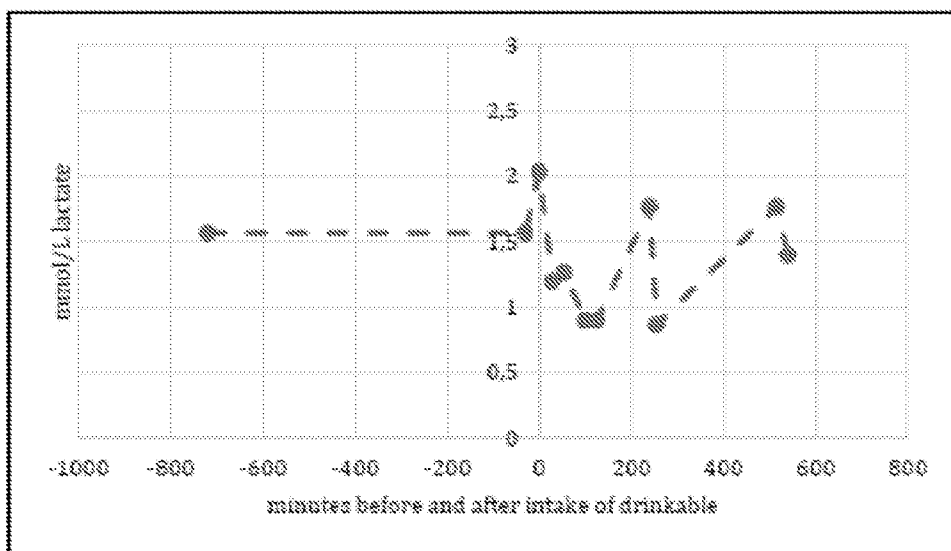


Figure 16

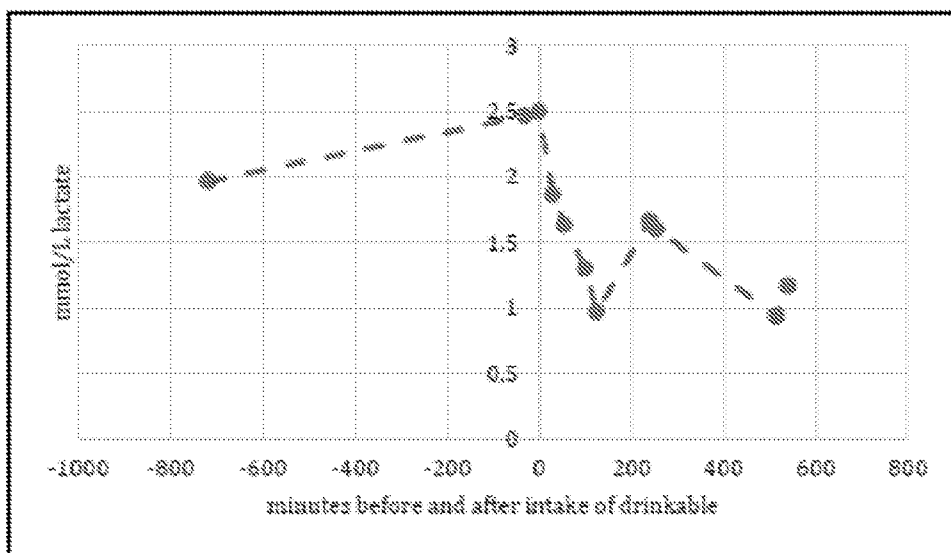


Figure 17

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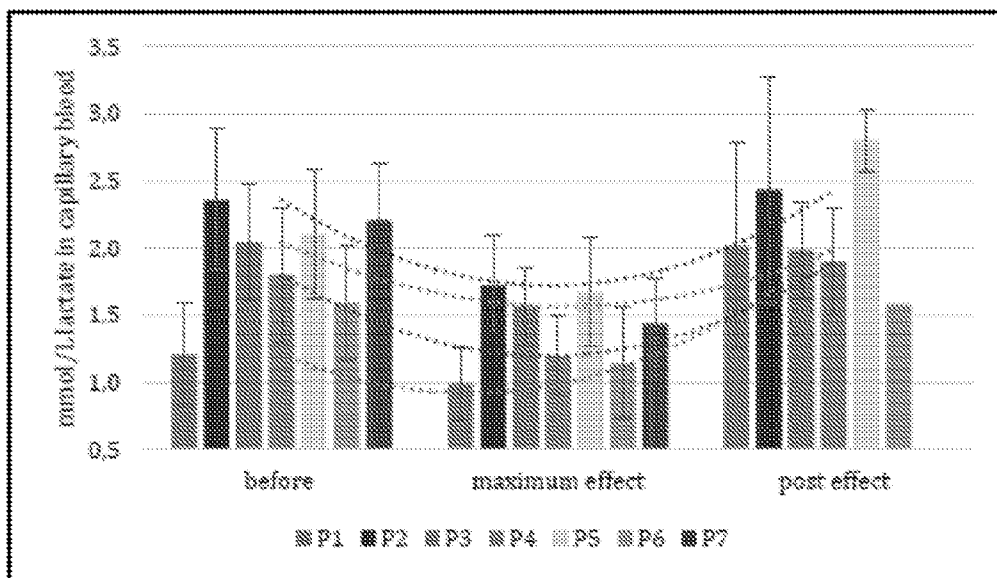


Figure 18

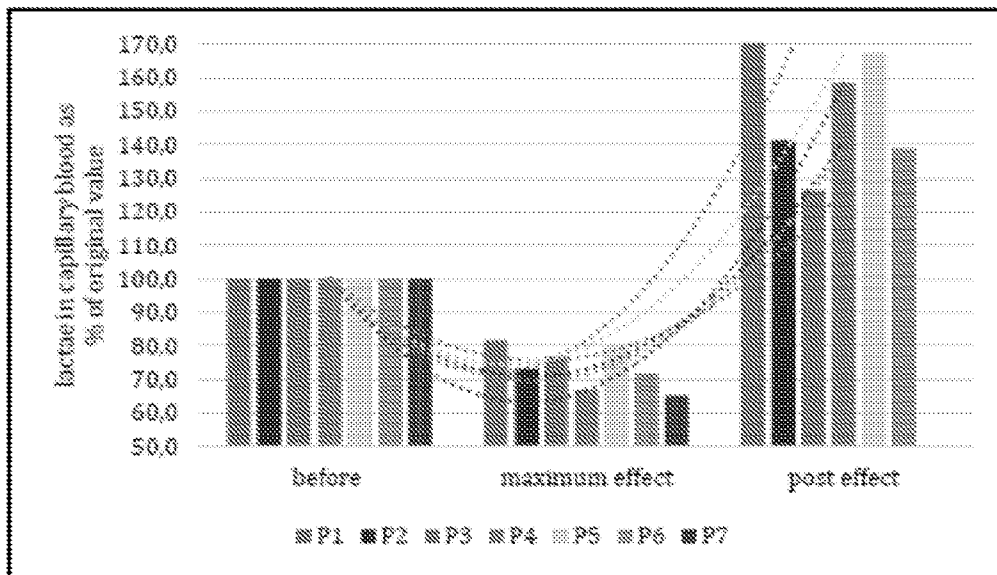


Figure 19

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Figure 22

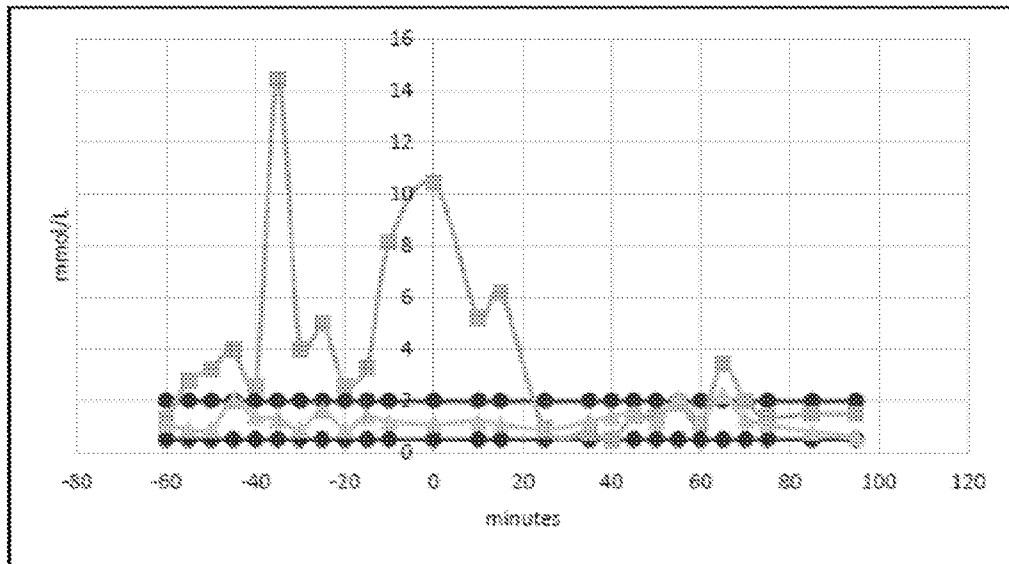
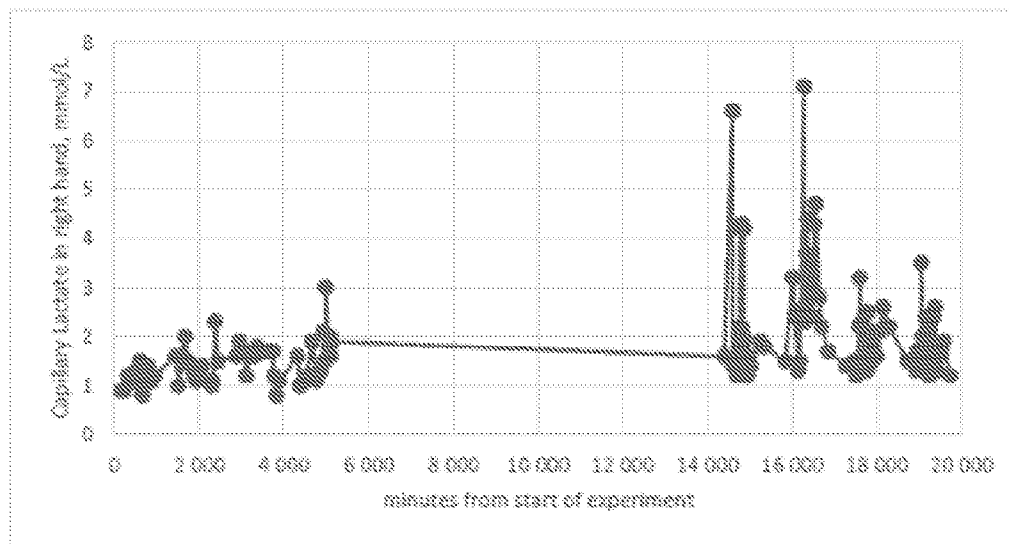


Figure 23



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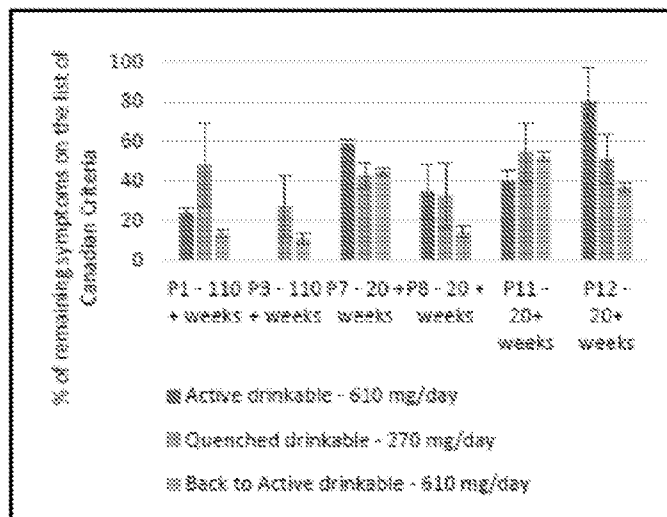


Figure 24

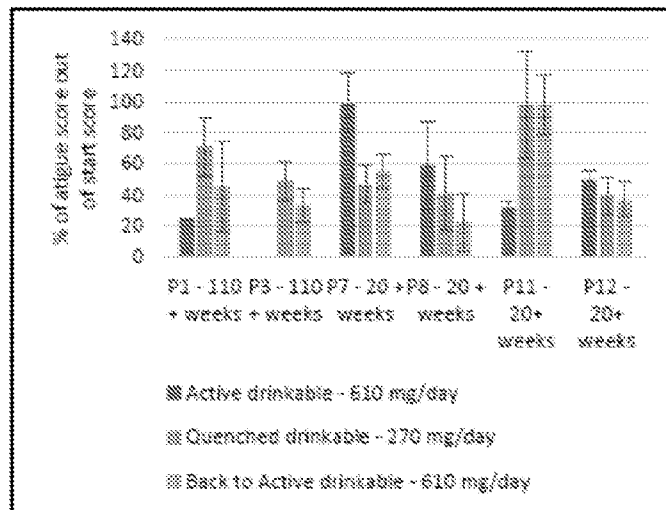


Figure 25

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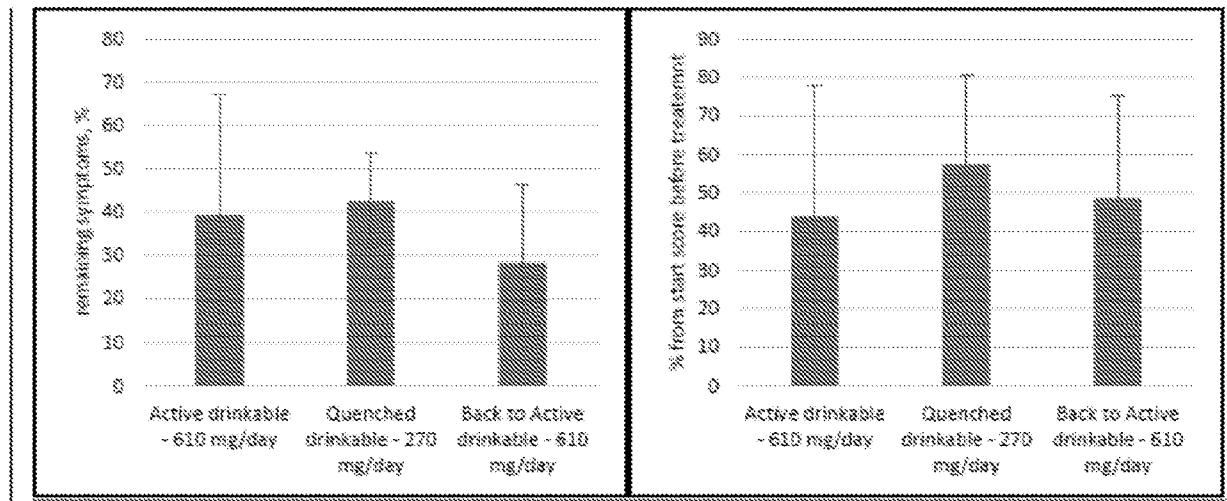


Figure 26

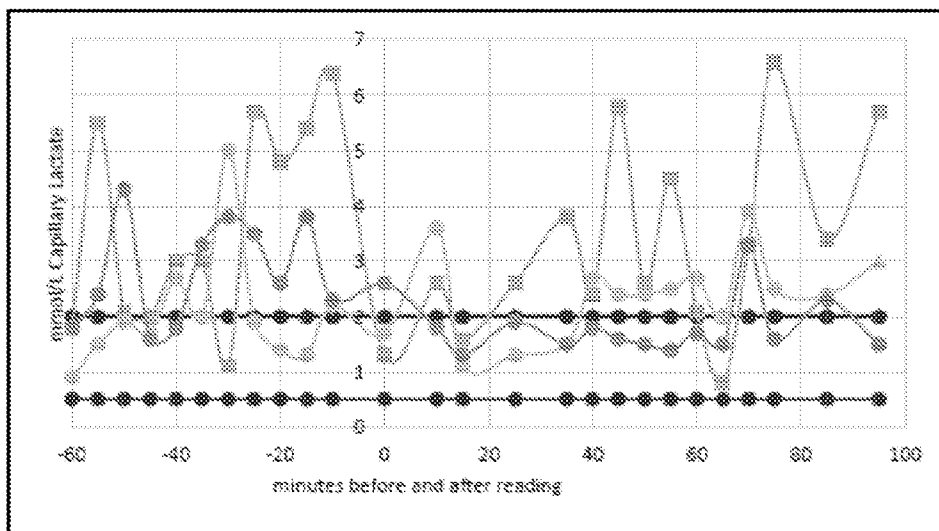


Figure 27

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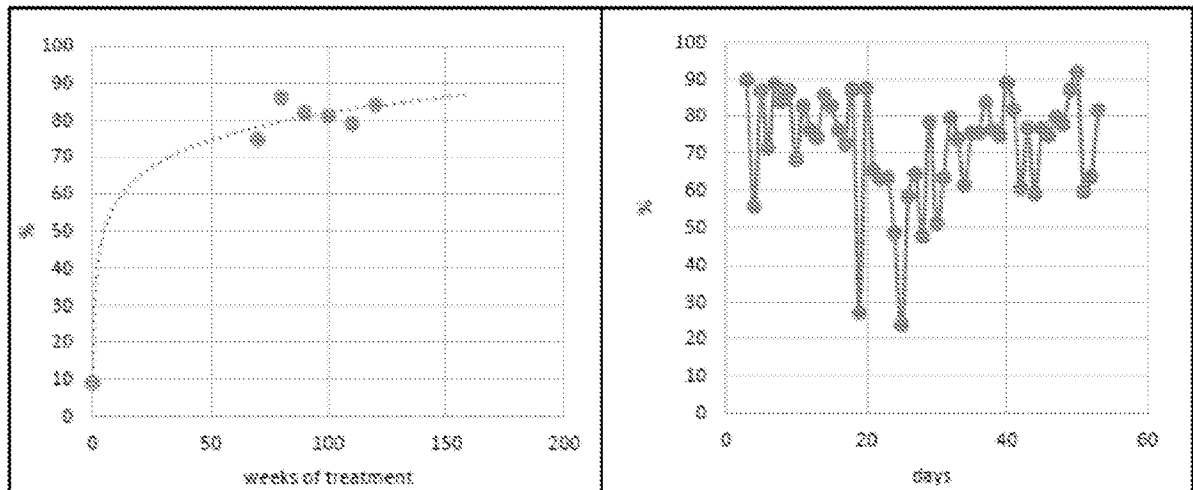


Figure 28A

Figure 28B

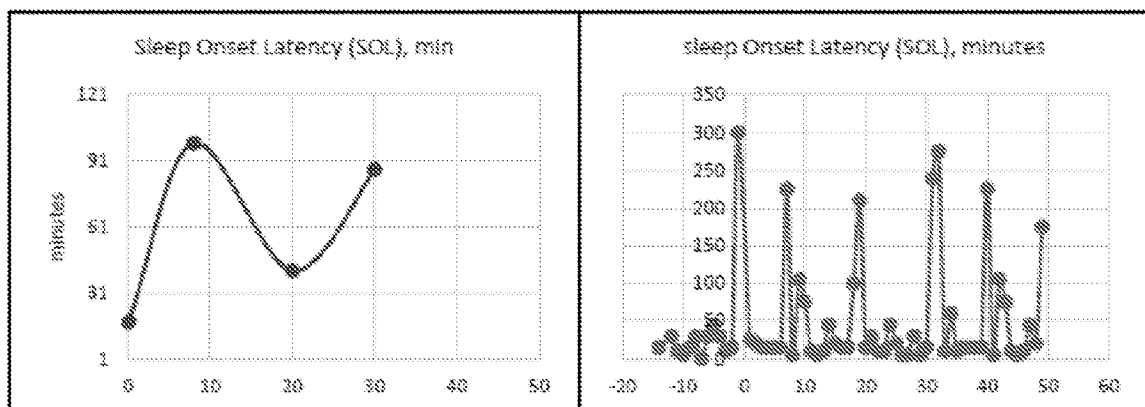


Figure 29A

Figure 29B

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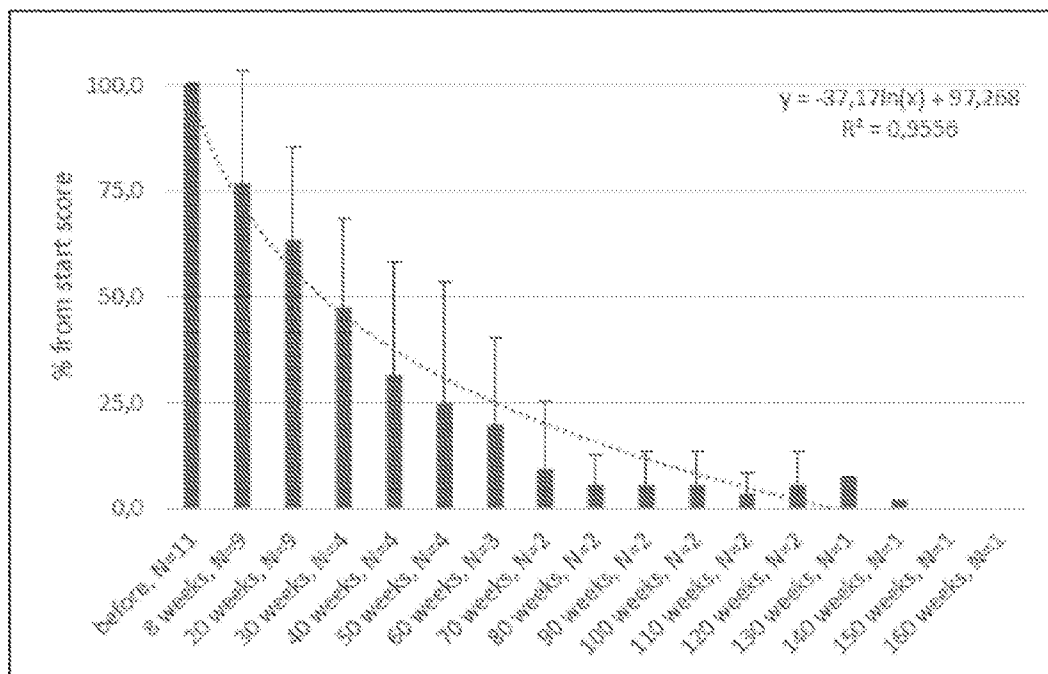


Figure 30

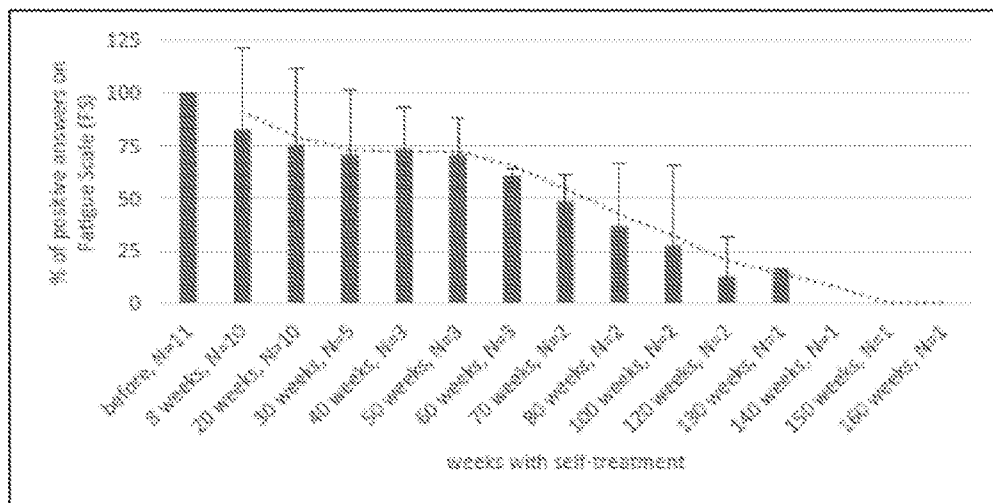


Figure 31

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Symptoms on the list of Canadian Criteria	Active drinkable, 100 ml	Active drinkable, 300 ml	Quenched drinkable, days	Back to Active drinkable again, days
1. Active drinkable, 100 ml	100	1		
2. Active drinkable, 300 ml				
3. Active drinkable, 100 ml				
4. Active drinkable, 300 ml				
5. Active drinkable, 100 ml				
6. Active drinkable, 300 ml				
7. Active drinkable, 100 ml				
8. Active drinkable, 300 ml				
9. Active drinkable, 100 ml				
10. Active drinkable, 300 ml				
11. Active drinkable, 100 ml				
12. Active drinkable, 300 ml				
13. Active drinkable, 100 ml				
14. Active drinkable, 300 ml				
15. Active drinkable, 100 ml				
16. Active drinkable, 300 ml				
17. Active drinkable, 100 ml				
18. Active drinkable, 300 ml				
19. Active drinkable, 100 ml				
20. Active drinkable, 300 ml				
21. Active drinkable, 100 ml				
22. Active drinkable, 300 ml				
23. Active drinkable, 100 ml				
24. Active drinkable, 300 ml				
25. Active drinkable, 100 ml				
26. Active drinkable, 300 ml				
27. Active drinkable, 100 ml				
28. Active drinkable, 300 ml				
29. Active drinkable, 100 ml				
30. Active drinkable, 300 ml				
31. Active drinkable, 100 ml				
32. Active drinkable, 300 ml				
33. Active drinkable, 100 ml				
34. Active drinkable, 300 ml				
35. Active drinkable, 100 ml				
36. Active drinkable, 300 ml				
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51. Active drinkable, 100 ml				
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57. Active drinkable, 100 ml				
58. Active drinkable, 300 ml				
59. Active drinkable, 100 ml				
60. Active drinkable, 300 ml				
61. Active drinkable, 100 ml				
62. Active drinkable, 300 ml				
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64. Active drinkable, 300 ml				
65. Active drinkable, 100 ml				
66. Active drinkable, 300 ml				
67. Active drinkable, 100 ml				
68. Active drinkable, 300 ml				
69. Active drinkable, 100 ml				
70. Active drinkable, 300 ml				
71. Active drinkable, 100 ml				
72. Active drinkable, 300 ml				
73. Active drinkable, 100 ml				
74. Active drinkable, 300 ml				
75. Active drinkable, 100 ml				
76. Active drinkable, 300 ml				
77. Active drinkable, 100 ml				
78. Active drinkable, 300 ml				
79. Active drinkable, 100 ml				
80. Active drinkable, 300 ml				
81. Active drinkable, 100 ml				
82. Active drinkable, 300 ml				
83. Active drinkable, 100 ml				
84. Active drinkable, 300 ml				
85. Active drinkable, 100 ml				
86. Active drinkable, 300 ml				
87. Active drinkable, 100 ml				
88. Active drinkable, 300 ml				
89. Active drinkable, 100 ml				
90. Active drinkable, 300 ml				
91. Active drinkable, 100 ml				
92. Active drinkable, 300 ml				
93. Active drinkable, 100 ml				
94. Active drinkable, 300 ml				
95. Active drinkable, 100 ml				
96. Active drinkable, 300 ml				
97. Active drinkable, 100 ml				
98. Active drinkable, 300 ml				
99. Active drinkable, 100 ml				
100. Active drinkable, 300 ml				

Table 17. Plus observations from P1. Rows cells depicting newly retained symptoms, as results of consumption of the Quenched drinkable and which described during 110 weeks of self-treatment with Active drinkable. It was only 4 symptoms on the list after 110 weeks of treatment. Five symptoms came back during 5 days on quenched drinkable. After exchange of the quenched drinkable back to active drinkable, eleven mentioned symptoms disappeared. By that we are the first to demonstrate, that described treatment reverse symptoms from the list of Canadian Criteria back and forward.

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Sample Rate on the list of Canadian Criteria	Active drinkable, weeks	Active drinkable, days	Quenched drinkable, days	Back to Active drinkable again, days
1	10	1	1	1
2	10	1	1	1
3	10	1	1	1
4	10	1	1	1
5	10	1	1	1
6	10	1	1	1
7	10	1	1	1
8	10	1	1	1
9	10	1	1	1
10	10	1	1	1
11	10	1	1	1
12	10	1	1	1
13	10	1	1	1
14	10	1	1	1
15	10	1	1	1
16	10	1	1	1
17	10	1	1	1
18	10	1	1	1
19	10	1	1	1
20	10	1	1	1
21	10	1	1	1
22	10	1	1	1
23	10	1	1	1
24	10	1	1	1
25	10	1	1	1
26	10	1	1	1
27	10	1	1	1
28	10	1	1	1
29	10	1	1	1
30	10	1	1	1
31	10	1	1	1
32	10	1	1	1
33	10	1	1	1
34	10	1	1	1
35	10	1	1	1
36	10	1	1	1
37	10	1	1	1
38	10	1	1	1
39	10	1	1	1
40	10	1	1	1
41	10	1	1	1
42	10	1	1	1
43	10	1	1	1
44	10	1	1	1
45	10	1	1	1
46	10	1	1	1
47	10	1	1	1
48	10	1	1	1
49	10	1	1	1
50	10	1	1	1
51	10	1	1	1
52	10	1	1	1
53	10	1	1	1
54	10	1	1	1
55	10	1	1	1
56	10	1	1	1
57	10	1	1	1
58	10	1	1	1
59	10	1	1	1
60	10	1	1	1
61	10	1	1	1
62	10	1	1	1
63	10	1	1	1
64	10	1	1	1
65	10	1	1	1
66	10	1	1	1
67	10	1	1	1
68	10	1	1	1
69	10	1	1	1
70	10	1	1	1
71	10	1	1	1
72	10	1	1	1
73	10	1	1	1
74	10	1	1	1
75	10	1	1	1
76	10	1	1	1
77	10	1	1	1
78	10	1	1	1
79	10	1	1	1
80	10	1	1	1
81	10	1	1	1
82	10	1	1	1
83	10	1	1	1
84	10	1	1	1
85	10	1	1	1
86	10	1	1	1
87	10	1	1	1
88	10	1	1	1
89	10	1	1	1
90	10	1	1	1
91	10	1	1	1
92	10	1	1	1
93	10	1	1	1
94	10	1	1	1
95	10	1	1	1
96	10	1	1	1
97	10	1	1	1
98	10	1	1	1
99	10	1	1	1
100	10	1	1	1

Table 18 Placebo-test, self-observations in person 3. Person had been on the self-treatment with Active drinkable for 210 weeks and reported no symptoms from the list of Canadian Criteria for last 90 weeks. During first 3 days with quenched drinkable 11 symptoms returned and severity of those and numbers increased to maximum 14 for 11 days. Right after five quenched drinkable was exchanged with active again, the symptoms diminished from the list and for 15 days reduced to none.

Symptoms on the list of Canadian CPGs	Active drinkable week	Active drinkable day	Quarantined drinkable days	Back to Active drinkable again, days
1	1	1	1	1
2	1	1	1	1
3	1	1	1	1
4	1	1	1	1
5	1	1	1	1
6	1	1	1	1
7	1	1	1	1
8	1	1	1	1
9	1	1	1	1
10	1	1	1	1
11	1	1	1	1
12	1	1	1	1
13	1	1	1	1
14	1	1	1	1
15	1	1	1	1
16	1	1	1	1
17	1	1	1	1
18	1	1	1	1
19	1	1	1	1
20	1	1	1	1
21	1	1	1	1
22	1	1	1	1
23	1	1	1	1
24	1	1	1	1
25	1	1	1	1
26	1	1	1	1
27	1	1	1	1
28	1	1	1	1
29	1	1	1	1
30	1	1	1	1
31	1	1	1	1
32	1	1	1	1
33	1	1	1	1
34	1	1	1	1
35	1	1	1	1
36	1	1	1	1
37	1	1	1	1
38	1	1	1	1
39	1	1	1	1
40	1	1	1	1
41	1	1	1	1
42	1	1	1	1
43	1	1	1	1
44	1	1	1	1
45	1	1	1	1
46	1	1	1	1
47	1	1	1	1
48	1	1	1	1
49	1	1	1	1
50	1	1	1	1
51	1	1	1	1
52	1	1	1	1
53	1	1	1	1
54	1	1	1	1
55	1	1	1	1
56	1	1	1	1
57	1	1	1	1
58	1	1	1	1
59	1	1	1	1
60	1	1	1	1
61	1	1	1	1
62	1	1	1	1
63	1	1	1	1
64	1	1	1	1
65	1	1	1	1
66	1	1	1	1
67	1	1	1	1
68	1	1	1	1
69	1	1	1	1
70	1	1	1	1
71	1	1	1	1
72	1	1	1	1
73	1	1	1	1
74	1	1	1	1
75	1	1	1	1
76	1	1	1	1
77	1	1	1	1
78	1	1	1	1
79	1	1	1	1
80	1	1	1	1
81	1	1	1	1
82	1	1	1	1
83	1	1	1	1
84	1	1	1	1
85	1	1	1	1
86	1	1	1	1
87	1	1	1	1
88	1	1	1	1
89	1	1	1	1
90	1	1	1	1
91	1	1	1	1
92	1	1	1	1
93	1	1	1	1
94	1	1	1	1
95	1	1	1	1
96	1	1	1	1
97	1	1	1	1
98	1	1	1	1
99	1	1	1	1
100	1	1	1	1
101	1	1	1	1
102	1	1	1	1
103	1	1	1	1
104	1	1	1	1
105	1	1	1	1
106	1	1	1	1
107	1	1	1	1
108	1	1	1	1
109	1	1	1	1
110	1	1	1	1
111	1	1	1	1
112	1	1	1	1
113	1	1	1	1
114	1	1	1	1
115	1	1	1	1
116	1	1	1	1
117	1	1	1	1
118	1	1	1	1
119	1	1	1	1
120	1	1	1	1
121	1	1	1	1
122	1	1	1	1
123	1	1	1	1
124	1	1	1	1
125	1	1	1	1
126	1	1	1	1
127	1	1	1	1
128	1	1	1	1
129	1	1	1	1
130	1	1	1	1
131	1	1	1	1
132	1	1	1	1
133	1	1	1	1
134	1	1	1	1
135	1	1	1	1
136	1	1	1	1
137	1	1	1	1
138	1	1	1	1
139	1	1	1	1
140	1	1	1	1
141	1	1	1	1
142	1	1	1	1
143	1	1	1	1
144	1	1	1	1
145	1	1	1	1
146	1	1	1	1
147	1	1	1	1
148	1	1	1	1
149	1	1	1	1
150	1	1	1	1
151	1	1	1	1
152	1	1	1	1
153	1	1	1	1
154	1	1	1	1
155	1	1	1	1
156	1	1	1	1
157	1	1	1	1
158	1	1	1	1
159	1	1	1	1
160	1	1	1	1
161	1	1	1	1
162	1	1	1	1
163	1	1	1	1
164	1	1	1	1
165	1	1	1	1
166	1	1	1	1
167	1	1	1	1
168	1	1	1	1
169	1	1	1	1
170	1	1	1	1
171	1	1	1	1
172	1	1	1	1
173	1	1	1	1
174	1	1	1	1
175	1	1	1	1
176	1	1	1	1
177	1	1	1	1
178	1	1	1	1
179	1	1	1	1
180	1	1	1	1
181	1	1	1	1
182	1	1	1	1
183	1	1	1	1
184	1	1	1	1
185	1	1	1	1
186	1	1	1	1
187	1	1	1	1
188	1	1	1	1
189	1	1	1	1
190	1	1	1	1
191	1	1	1	1
192	1	1	1	1
193	1	1	1	1
194	1	1	1	1
195	1	1	1	1
196	1	1	1	1
197	1	1	1	1
198	1	1	1	1
199	1	1	1	1
200	1	1	1	1
201	1	1	1	1
202	1	1	1	1
203	1	1	1	1
204	1	1	1	1
205	1	1	1	1
206	1	1	1	1
207	1	1	1	1
208	1	1	1	1
209	1	1	1	1
210	1	1	1	1
211	1	1	1	1
212	1	1	1	1
213	1	1	1	1
214	1	1	1	1
215	1	1	1	1
216	1	1	1	1
217	1	1	1	1
218	1	1	1	1
219	1	1	1	1
220	1	1	1	1
221	1	1	1	1
222	1	1	1	1
223	1	1	1	1
224	1	1	1	1
225	1	1	1	1
226	1	1	1	1
227	1	1	1	1
228	1	1	1	1
229	1	1	1	1
230	1	1	1	1
231	1	1	1	1
232	1	1	1	1
233	1	1	1	1
234	1	1	1	1
235	1	1	1	1
236	1	1	1	1
237	1	1	1	1
238	1	1	1	1
239	1	1	1	1
240	1	1	1	1
241	1	1	1	1
242	1	1	1	1
243	1	1	1	1
244	1	1	1	1
245	1	1	1	1
246	1	1	1	1
247	1	1	1	1
248	1	1	1	1
249	1	1	1	1
250	1	1	1	1
251	1	1	1	1
252	1	1	1	1
253	1	1	1	1
254	1	1	1	1
255	1	1	1	1
256	1	1	1	1
257	1	1	1	1
258	1	1	1	1
259	1	1	1	1
260	1	1	1	1
261	1	1	1	1
262	1	1	1	1
263	1	1	1	1
264	1	1	1	1
265	1	1	1	1
266	1	1	1	1
267	1	1	1	1
268	1	1	1	1
269	1	1	1	1
270	1	1	1	1
271	1	1	1	1
272	1	1	1	1
273	1	1	1	1
274	1	1	1	1
275	1	1	1	1
276	1	1	1	1
277	1	1	1	1
278	1	1	1	1
279	1	1	1	1
280	1	1	1	1
281	1	1	1	1
282	1	1	1	1
283	1	1	1	1
284	1	1	1	1
285	1	1	1	1
286	1	1	1	1
287	1	1	1	1
288	1	1	1	1
289	1	1	1	1
290	1	1	1	1
291	1	1	1	1
292	1	1	1	1
293	1	1	1	1
294	1	1	1	1
295	1	1	1	1
296	1	1	1	1
297	1	1	1	1
298	1	1	1	1
299	1	1	1	1
300	1	1	1	1
301	1	1	1	1
302	1	1	1	1
303	1	1	1	1
304	1	1	1	1
305	1	1	1	1
306	1	1	1	1
307	1	1	1	1
308	1	1	1	1
309	1	1	1	1
310	1	1	1	1
311	1	1	1	1
312	1	1	1	1
313	1	1	1	1
314	1	1	1	1
315	1	1	1	1
316	1	1	1	1
317	1	1	1	1
318	1	1	1	1
319	1	1	1	1
320	1	1	1	1
321	1	1	1	1
322	1	1	1	1
323	1	1	1	1
324	1	1	1	1
325	1	1	1	1
326	1	1	1	1
327	1	1	1	1
328	1	1	1	1
329	1	1	1	1
330	1	1	1	1
331	1	1	1	1
332	1	1	1	1
333	1	1	1	1
334	1	1	1	1
335	1	1	1	1
336	1	1	1	1
337	1	1	1	1
338	1	1	1	1
339	1	1	1	1
340	1	1	1	1
341	1	1	1	

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Symptoms on the List of Canadian Criteria	Active drinks used	Active drinks, days	Quenched drinks, days	Back to Active drinks again, days
1	30	1	1	1
2	30	1	1	1
3	30	1	1	1
4	30	1	1	1
5	30	1	1	1
6	30	1	1	1
7	30	1	1	1
8	30	1	1	1
9	30	1	1	1
10	30	1	1	1
11	30	1	1	1
12	30	1	1	1
13	30	1	1	1
14	30	1	1	1
15	30	1	1	1
16	30	1	1	1
17	30	1	1	1
18	30	1	1	1
19	30	1	1	1
20	30	1	1	1
21	30	1	1	1
22	30	1	1	1
23	30	1	1	1
24	30	1	1	1
25	30	1	1	1
26	30	1	1	1
27	30	1	1	1
28	30	1	1	1
29	30	1	1	1
30	30	1	1	1
31	30	1	1	1
32	30	1	1	1
33	30	1	1	1
34	30	1	1	1
35	30	1	1	1
36	30	1	1	1
37	30	1	1	1
38	30	1	1	1
39	30	1	1	1
40	30	1	1	1
41	30	1	1	1
42	30	1	1	1
43	30	1	1	1
44	30	1	1	1
45	30	1	1	1
46	30	1	1	1
47	30	1	1	1
48	30	1	1	1
49	30	1	1	1
50	30	1	1	1
51	30	1	1	1
52	30	1	1	1
53	30	1	1	1
54	30	1	1	1
55	30	1	1	1
56	30	1	1	1
57	30	1	1	1
58	30	1	1	1
59	30	1	1	1
60	30	1	1	1
61	30	1	1	1
62	30	1	1	1
63	30	1	1	1
64	30	1	1	1
65	30	1	1	1
66	30	1	1	1
67	30	1	1	1
68	30	1	1	1
69	30	1	1	1
70	30	1	1	1
71	30	1	1	1
72	30	1	1	1
73	30	1	1	1
74	30	1	1	1
75	30	1	1	1
76	30	1	1	1
77	30	1	1	1
78	30	1	1	1
79	30	1	1	1
80	30	1	1	1
81	30	1	1	1
82	30	1	1	1
83	30	1	1	1
84	30	1	1	1
85	30	1	1	1
86	30	1	1	1
87	30	1	1	1
88	30	1	1	1
89	30	1	1	1
90	30	1	1	1
91	30	1	1	1
92	30	1	1	1
93	30	1	1	1
94	30	1	1	1
95	30	1	1	1
96	30	1	1	1
97	30	1	1	1
98	30	1	1	1
99	30	1	1	1
100	30	1	1	1

Table 20. Placebo-test, self-observations from user 7. Blue cells depict symptoms in fluctuation, as results of consumption of Quenched drinks. This person had prolonged response time to lowering of the osalates dose. After the test P7 chosen to continue self-treatment on lower dose of osalates and reporting significant improvement.

Table 21. Placebo-test, self-observations from user 11. Blue cells depict symptoms in fluctuation, as results of consumption of Quenched drinkable. Brown cells are symptoms gained back as result of lowered dose of exolates. Two symptoms came back on the 1st during 14 days on Quenched drinkable and disappeared again when P13 changed back to Active drinkable.

Symptoms on the List of Canadian Criteria	Active drinking, weeks	Active drinking, days	Completed drinking, days	Back to Active drinking again, days
1	1	1	1	1
2	1	1	1	1
3	1	1	1	1
4	1	1	1	1
5	1	1	1	1
6	1	1	1	1
7	1	1	1	1
8	1	1	1	1
9	1	1	1	1
10	1	1	1	1
11	1	1	1	1
12	1	1	1	1
13	1	1	1	1
14	1	1	1	1
15	1	1	1	1
16	1	1	1	1
17	1	1	1	1
18	1	1	1	1
19	1	1	1	1
20	1	1	1	1
21	1	1	1	1
22	1	1	1	1
23	1	1	1	1
24	1	1	1	1
25	1	1	1	1
26	1	1	1	1
27	1	1	1	1
28	1	1	1	1
29	1	1	1	1
30	1	1	1	1
31	1	1	1	1
32	1	1	1	1
33	1	1	1	1
34	1	1	1	1
35	1	1	1	1
36	1	1	1	1
37	1	1	1	1
38	1	1	1	1
39	1	1	1	1
40	1	1	1	1
41	1	1	1	1
42	1	1	1	1
43	1	1	1	1
44	1	1	1	1
45	1	1	1	1
46	1	1	1	1
47	1	1	1	1
48	1	1	1	1
49	1	1	1	1
50	1	1	1	1
51	1	1	1	1
52	1	1	1	1
53	1	1	1	1
54	1	1	1	1
55	1	1	1	1
56	1	1	1	1
57	1	1	1	1
58	1	1	1	1
59	1	1	1	1
60	1	1	1	1
61	1	1	1	1
62	1	1	1	1
63	1	1	1	1
64	1	1	1	1
65	1	1	1	1
66	1	1	1	1
67	1	1	1	1
68	1	1	1	1
69	1	1	1	1
70	1	1	1	1
71	1	1	1	1
72	1	1	1	1
73	1	1	1	1
74	1	1	1	1
75	1	1	1	1
76	1	1	1	1
77	1	1	1	1
78	1	1	1	1
79	1	1	1	1
80	1	1	1	1
81	1	1	1	1
82	1	1	1	1
83	1	1	1	1
84	1	1	1	1
85	1	1	1	1
86	1	1	1	1
87	1	1	1	1
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INTERNATIONAL SEARCH REPORT

International application No

PCT/N02017/000033

A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61K31/194 A61K31/195 A61P3/00
 ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.



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Date of the actual completion of the international search

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Date of mailing of the international search report

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040,
 Fax: (+31-70) 340-3016

Authorized officer

Uryga-Polowy, V

INTERNATIONAL SEARCH REPORT

International application No

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