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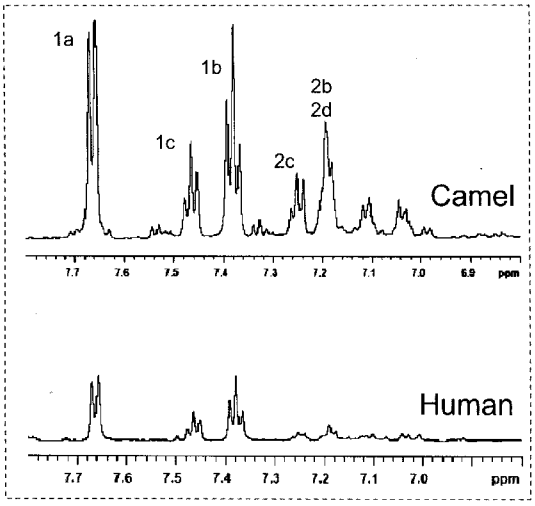
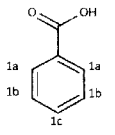
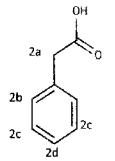
(54) Title: BIOACTIVE COMPOUNDS IN CAMEL URINE AND MILK

Fig. 1A





Benzoate



Phenylacetate

(57) Abstract: The present document describes extracts from camel urine and/or milk comprising benzoate, phenylacetate and other molecular species. Also described are methods of use of the extracts and the identified compounds for the treatment of diseases, and methods of isolating the extracts.

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Title: **BIOACTIVE COMPOUNDS IN CAMEL URINE AND MILK**

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority from US provisional patent applications 61/373,300, filed August 13; 2010, and 61/384,516, filed September 20, 2010 the specifications of which is hereby incorporated by reference.

BACKGROUND

(a) Field

[0002] The subject matter disclosed generally relates to extracts from camel urine and milk. More specifically, the subject matter relates to bioactive extracts from camel urine comprising benzoate; phenylacetate and several other molecular species.

(b) Related Prior Art

[0003] The use of animal urine and milk as a source of therapeutic ingredients has been known for centuries. The use of camel urine in traditional Arab medicine has been well acknowledged since pre-medieval era, as best documented by several authors including Avicenna who, in the book "laws of medicine" described a number of medicinal ingredients from various plant and animal sources including those from human and camel urines [Avicena or Ibn Sina "Qanun fi-al-tibb" (http://almashriq.hiof.no/ddc/projects/saab/avicenna/896/html/S1_005.html)], and Prioreschi, 2001, Horatius press, Omaha, Nebraska).

[0004] Despite the acknowledgement of its medicinal properties, the various bioactive molecules in human urine have not yet been thoroughly characterized. This is surprising since it is now well established that urine contains many biomedically relevant compounds namely hormones, growth factors and neuropeptides. The most outstanding of those are premarin consisting of conjugated estrogens extracted from pregnant mare's urine (Stefanick, M.L., 2005, *Am. J. Med.* 118 Suppl 12B, 64-73), one of the most prescribed drugs in the USA used in hormone replacement therapy. Another

one is human chorionic gonadotropin (hCG) approved since more than 40 years for clinical treatment of infertility where it is used to induce ovulation or stimulate testicular development and spermatogenesis. Of particular importance is the characterization of anti-cancer molecules in human urine which contains low molecular weight compounds which we named HIP (HCG-like Inhibitory Products) purified from urine extracts of pregnant women which potently block the growth of tumour cells in HIV-related Kaposi sarcoma (Kachra et al., 1997, *Endocrinology* 138, 4038-4041).

[0005] The urine of the camel is of particular interest. Desert Bedouins in Asia are known to use camel urine and milk for healing several diseases such as fever, infections, abdominal swelling, liver diseases and a variety of other ailments (Guthier-Pilters and Dagg, 1981, University of Chicago Press, Chicago; Prioreschi, 2001, Horatius press, Omaha, Nebraska). Such healing properties of camel urine and milk are particularly reported in Islamic literature called "Hadith" (Guthier-Pilters and Dagg, 1981, University of Chicago Press, Chicago; Prioreschi, 2001, Horatius press, Omaha, Nebraska) , Although these claims remain to be substantiated by scientific proof. Some of these medicinal ingredients are used even today. For example, it has been witnessed that in Saudi Arabia, people come to camel sheppards on the side of local highways to purchase urine and milk for consumption as medicinal products.

[0006] The physiology of camels is interesting. Arabian camels are called the desert ships because they can walk in the desert for days without drinking and can withstand extreme high temperature of 40°C. Camels not only survive the harsh hot weather but also resist many viral and other infections presumably due to the unique molecular composition of their immunoglobulins (Deschacht et al., 2010, *J. Immunol.* 184, 5696-5704). It is believed that the camel's peculiar natural antibodies display a wide antigen-recognizing repertoire may be responsible for infection resistance. It is suggested that camels display very low rates of water excretion as compared to other animals who share the same habitat (donkeys, horses, sheep)

Guthier-Pilters and Dagg, 1981, University of Chicago Press, Chicago). This results in the concentration of solutes and metabolites in the urine. Since camels do not urinate for a long time, their urine represents a valuable source of metabolites.

[0007] There is a need for bioactive compounds isolated from camel urine.

[0008] There is a need for bioactive compounds isolated from camel urine for the treatment of diseases, including cancers.

SUMMARY

[0009] According to an embodiment, there is provided an extract from camel urine comprising an NMR spectrum as set forth in figure 1.

[0010] According to an embodiment, there is provided an extract from camel urine comprising a HPLC fractionation spectrum as set forth in figure 8A.

[0011] The extract may comprise a fraction C of said HPLC fractionation spectrum as set forth in figure 8A.

[0012] According to another embodiment, there is provided extract from camel milk comprising at least one compound chosen from benzoate, lactate and citrate.

[0013] The extract may be further comprising at least one compound chosen from acetoacetic acid, fumaric acid, glyceric acid, homovanillic acid, oxalic acid, oxoprolic acid, phenylpyruvic acid, propionylglycinic acid, pyruvic acid, 2-hydroxyglutaric acid, 2-oxoadipic acid, 2-oxoglutaric, 3-hydroxybutiric acid, 3 hydroxypropionic acid, 4-hydroxyphenyllactic acid, and 4-hydroxyphenylpyruvic acid.

[0014] According to another embodiment, there is provided a pharmaceutical composition comprising an extract from camel urine, camel milk, or combination thereof and a pharmaceutically acceptable carrier.

[0015] According to another embodiment, there is provided a pharmaceutical composition comprising at least one compound as identified by a peak of an NMR spectrum as set forth in figure 1, a HPLC fractionation spectrum as set forth in figure 8A or a fraction C thereof; and a pharmaceutically acceptable carrier.

[0016] According to another embodiment, there is provided a use of an extract from camel urine, camel milk, or combination thereof for the preparation of a medicament for the treatment of a disease.

[0017] According to another embodiment, there is provided a use of an extract from camel urine, camel milk, or combination thereof for the treatment of a disease.

[0018] According to another embodiment, there is provided a use of at least one compound as identified by a peak of an NMR spectrum as set forth in figure 1, a HPLC fractionation spectrum as set forth in figure 8A or a fraction C thereof for the preparation of a medicament for the treatment of a disease.

[0019] According to another embodiment, there is provided a use of at least one compound as identified by a peak of an NMR spectrum as set forth in figure 1, a HPLC fractionation spectrum as set forth in figure 8A or a fraction C thereof for the treatment of a disease.

[0020] The at least one compound may be benzoate, phenylacetate or a combination thereof. The at least one compound may be chosen from Butyrylglycinic acid, Citric acid, Ethylmalonic acid, Glyceric acid, Glycolic acid, Glutaric acid, Hexanoylglycenic acid, Hippuric acid, Homovanillic acid Homogentisic acid, Isobutyrylglycinic acid, Isovalerylglycinic acid, Lactic acid, Malonic acid, Methylcitric acid, Methylmalonic acid, Methylsuccinic acid, N-acetylaspartic acid, Oxalic acid, Oxoprolinic (pyroglutamic) acid, Phenylpropioniglycinic acid, Phenyllactic, Propionylglycinic acid, Pyruvic acid, Sebacic acid, Suberic acid, 2-hydroxyadipic acid, 2-hydroxyglutaric acid, 2-hydroxyisovaleric acid, 2-hydroxyphenylacetic acid, 2-methyl-3-hydroxybutiric

acid, 2-methylacetoacetique acid, 2-methylbutyrylglycinic acid, 3-hydroxyisovaleric acid, 3-hydroxy-3-methylglutaric acid, 3-hydroxybutyric acid, 3-hydroxypropionic acid, 3-methylcrotonylglycinic acid, 3-methylglutaconic acid, 4-hydroxyphenylacetic acid, 4-hydroxyphenyllactic acid.

[0021] The disease may be a cancer, a neoplasm including multidrug resistant tumors, various haematological malignancies, and the cancer may be chosen from a breast cancer, colon cancer, a prostate cancer, malignant gliomas, and a thyroid cancer .

[0022] The disease may be a metabolic defect in a urea-cycle enzyme.

[0023] The disease may be any metabolic disease such as diabetes or pathologic obesity that is regulated by the Peroxisome Proliferator-activiated Receptor (PPAR) which belongs to the steroid receptor superfamily

[0024] The disease may be any metabolic disease such as diabetes or pathologic obesity that is regulated or by the DNA binding partner of the Peroxisome Proliferator-activiated Receptor (PPAR) which is the retinoid X receptors (RXR),

[0025] The disease may be chosen from multiple sclerosis, sickle cell anaemia, amyotrophic lateral sclerosis, and Huntington's disease.

[0026] According to another embodiment, there is provided a method of treating a disease in a subject in need thereof by administering to the subject a therapeutically effective amount of an extract camel urine, camel milk, or combination thereof.

[0027] According to another embodiment, there is provided a method of treating a disease in a subject in need thereof by administering to the subject a therapeutically effective amount of at least one compound as identified by a peak of an NMR spectrum as set forth in figure 1, a HPLC fractionation spectrum as set forth in figure 8A or a fraction C thereof.

[0028] The compound may be benzoate, phenylacetate or a combination thereof. The at least one compound may be chosen from

Butyrylglycinic acid, Citric acid, Ethylmalonic acid, Glyceric acid, Glycolic acid, Glutaric acid, Hexanoylglycenic acid, Hippuric acid, Homovanillic acid Homogentisic acid, Isobutyrylglycinic acid, Isovalerylglycinic acid, Lactic acid, Malonic acid, Methylcitric acid, Methylmalonic acid, Methylsuccinic acid, N-acetylaspartic acid, Oxalic acid, Oxoprolinic (pyroglutamic) acid, Phenylpropioniglycinic acid, Phenyllactic, Propionylglycinic acid, Pyruvic acid, Sebacic acid, Suberic acid, 2-hydroxyadipic acid, 2-hydroxyglutaric acid, 2-hydroxyisovaleric acid, 2-hydroxyphenylacetic acid, 2-methyl-3-hydroxybutiric acid, 2-methylacetoacetique acid, 2-methylbutyrylglycinic acid, 3-hydroxyisovaleric acid, 3-hydroxy-3-methylglutaric acid, 3-hydroxybutyric acid, 3-hydroxypropionic acid, 3-methylcrotonylglycinic acid, 3-methylglutaconic acid, 4-hydroxyphenylacetic acid, 4-hydroxyphenyllactic acid, and retinoid derivative such as 9-cis retinoic acid.

[0029] The disease may be a cancer, a neoplasm, a multidrug resistant tumors, a haematological malignancy, and the cancer may be a breast cancer, a colon cancer, a prostate cancer, a malignant glyoma, and a thyroid cancer.

[0030] The disease may be a metabolic defect in a urea-cycle enzyme.

[0031] The disease may be chosen from multiple sclerosis, sickle cell anemia, amyotrophic lateral sclerosis, and Huntington's disease.

[0032] According to another embodiment, there is provided a method of producing an extract from camel urine comprising an NMR spectrum as defined in figure 1 by removing a fraction of at least 10 kDa from a camel urine sample to produce an extract having at least one molecule of molecular weight lower than 10 kDa.

[0033] The removal of the molecules may be done by filtration of said camel urine sample. The filtration may be with a filter membrane. The filter membrane may have pores preventing passage of molecules having at least 10 kDa or more. The filter membrane may be treated with water prior to filtration of said camel urine sample.

[0034] The following terms are defined below.

[0035] The term "molecular weight cut-off" or cut-off value is defined as the molecular weight at which a where the membrane or filter will reject, or prevent the passage of 90% of the solutes. Hence, a filter with a molecular weight cut-off of about 10 kDa will prevent the passage of molecules having molecular weight of at least 10 kDa.

[0036] The term "pharmaceutically acceptable carrier" is intended to mean a preservative solution, a saline solution, an isotonic (about 0.9%) saline solution, or about a 5% albumin solution, suspension, sterile water, phosphate buffered saline, and the like. Other buffering agents, dispersing agents, and inert non-toxic substances suitable for delivery to a patient may be included in the compositions of the present invention. The compositions may be solutions, suspensions or any appropriate formulation suitable for administration, and are typically sterile and free of undesirable particulate matter. The compositions may be sterilized by conventional sterilization techniques.

[0037] The term "nutraceutical" is intended to mean a food or food product that provides health and medical benefits, including the prevention and treatment of disease.

[0038] The term "a non-food ingredient" is intended to mean an ingredient that may be added to food but that may not be a food ingredient contributing to the caloric content of the food *per se*.

[0039] Features and advantages of the subject matter hereof will become more apparent in light of the following detailed description of selected embodiments, as illustrated in the accompanying figures. As will be realized, the subject matter disclosed and claimed is capable of modifications in various respects, all without departing from the scope of the claims. Accordingly, the drawings and the description are to be regarded as illustrative in nature, and not as restrictive and the full scope of the subject matter is set forth in the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] Further features and advantages of the present disclosure will become apparent from the following detailed description, taken in combination with the appended drawings, in which:

[0041] Fig. 1 illustrates the ^{1}H NMR spectra of camel urine compared to human urine. The full spectra are shown in the lower part of the figure. The expanded spectra of the region 7.1-7.9 (boxed area) are shown on the top. The phenylacetate and benzoate NMR peaks are more intense in camel than human. The numbers 1a, 1b, 1c and 2b, 2c, 2d refer to the characteristic peaks emanating from the carbons identified by the same numbers on the chemical atomic structures shown. Other compounds labeled by the indicated numbers correspond to the chemicals shown in the boxed area. Creatinine, which constitutes a standard reference in urine analysis, is also shown. The star (*) identified peak is present only in camel but not human.

[0042] Figs. 2A and 2B illustrate the GS-MS spectra of benzoic acid and phenylacetic acid identified in camel urine using GS-MS. Fig. 2A shows the entire spectrum of camel urine. Fig. 2B shows spectra identified in camel urine. Right panel shows the mass spectrum of benzoic acid on EI ionization, showing molecular ions $C_7H_6O_2^{\bullet+}$ at m/z= 122, $C_6H_5CO^+$ benzoyl ions at m/z=105, $C_6H_5^+$ ions at m/z=77 and $C_4H_3^+$ ions at m/z=51. Left panel corresponds to phenylacetic acid on EI ionization, showing molecular ions $C_8H_8O_2^+$ at m/z=136 and strong peak at m/z=91which is characterized by $C_6H_5CH_2^+$ ions.

[0043] Fig. 3 illustrates the mechanisms of ammonia diversion from the urea cycle with the administration of phenylacetate and benzoate.

[0044] Figs. 4A and 4B illustrates (A) the fractionation of camel urine using reversed phase-HPLC and (B) the bioassay of the collected fractions following HPLC separation. Panel A shows the elution profile of camel urine from the HPLC column. Y axis indicates absorbency at 220 nm. x-axis indicated time of elution in minutes. The contents of the indicated elution tubes are pooled into five fractions named A, B, C, D, E, then lyophilized.

Panel B shows the bioactivity of the five fractions as tested *in vitro* for cell proliferation using the MCF7 cells. Y-axis shows % cell proliferation of the test material as compared to the Vehicle (Veh), i.e a control consisting of culture media alone.

[0045] It will be noted that throughout the appended drawings, like features are identified by like reference numerals.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0046] In embodiments there is disclosed an extract from camel urine. The extract of the present invention of the present invention comprise the NMR spectrum as defined in Fig. 1.

[0047] Referring now to Fig. 1, a ^{1}H NMR spectra of camel urine showing significant differences as compared to human urine. The most striking finding in the camel urine is marked, high levels of both benzoate and phenylacetate (Fig. 1). In contrast, human, rat, elephant and dromedary urines display very little expression of these two compounds as shown in Table 1.

Table 1. Concentrations of four relevant metabolites in the urine of three adult male camels as compared to the corresponding average values in human *. Values are expressed in µmol/mmol of creatinine

	Benzoate	Phenylacetate	Hippurate	Citrate
Camel 1	794	85	91	2
Camel 2	1374	28	6436	11
Camel 3	2284	47	2166	BDL
Human	2	BDL	252	311
Elephant	9	2	9836	UD
Dromedary 1	3	UD	7285	UD
Dromedary 2	6	UD	5790	3
Rat	2	1	507	1833

Notes:* The numbers shown for "human" are average values in urines from 13 adult men (average age 34). UD: means undetectable. Actual values are shown in Table 2

[0048] The number of NMR signals in camel urines is much less than the corresponding signal numbers in human urines. The spectra show that the camel urine has lower level of sugar compared to human samples. More notable is the presence of peaks that are only present in camel urine. For example, an intense peak around 5.3 ppm is always present in the camel urine spectra and it is absent from any human urine spectra, indicating that some metabolites are unique to camel. Other intense peaks appear at 1.85 ppm, 2.255 ppm, 2.93 ppm, 3.205 and 3.91 ppm repeatedly demonstrated in camel spectra.

[0049] While the urea peak is quite comparable in camel and human urine, creatinine and citrate signals demonstrate higher concentration in human urine than camel. NMR results show that the level of benzoate (benzoic acid) in camel urine is higher than in human urine. Similarly, for phenylacetate there is a significant difference between camel and human. In contrast, the creatinine level in human urine is slightly higher than camel. Quantitative assays are done using established methods according to Sweetman, 1990. After normalizing the creatinine level we found that camel

contains remarkably more benzoate than human (Table 1). Similarly, phenylacetate is significantly higher in camel (Table 1). The results confirm that the detected metabolites in camel urine have a unique profile with respect to their type, number and concentrations. The high level of benzoate and phenylacetate represent an exceptional difference of camel urine.

[0050] The clinical use of phenylacetate (PA) and benzoate in lowering plasma ammonium levels in patients with hyperammonemia represent the hallmark of their therapeutic action (Enns *et al.*, 2007, *N. Engl. J. Med.* 356, 2282-2292). In certain metabolic diseases resulting from defects in urea-cycle enzymes, ammonium which cannot be converted to urea accumulates to a toxic level that can be lethal. This drug combination of PA and benzoate, marketed as Ammonul®, is useful to treat patients with inborn errors of metabolism of the urea-cycle enzyme and prevents several complications such as encephalopathy and death (Enns *et al.*, 2007, *N. Engl. J. Med.* 356, 2282-2292). In fact, phenylacetate, through mitochondrial conjugation with glutamine, results in phenylacetyglutamine. Similarly, benzoate combines with glycine thus forming benzoylglycine (hippurate) (see Fig. 3). These two non-toxic compounds are easily eliminated in the urine. Using this well established drug combination consisting of phenylacetate and benzoate, Enns (Enns *et al.*, 2007, *N. Engl. J. Med.* 356, 2282-2292) reported results of a 25 year clinical study demonstrating an overall survival of 84 % following the treatment.

[0051] In addition to their usefulness in treating urea cycle enzyme defects, both phenylacetate and benzoate are found to be potentially useful for the treatment of multiple sclerosis, as disease characterized by demyelination presumably due to a T-cell auto-immune response. In a mouse model of multiple sclerosis (Brahmachari *et al.*, 2009, *J. Immunol.* 183, 5917-5927), both compounds exert immunomodulatory and anti-inflammatory effects which are mediated by immune T-cells and involve among others, suppression of NF-κB and nitric oxide synthetase; these actions ultimately result in the alleviation of the disease.

[0052] Phenylacetate (PA) and phenylbutyrate (PB), the parent compound from which it is metabolized in humans and animals, both display other important bioactivities other than those cited above. Chemically, these metabolites (PA and PB) belong to a group of aromatic fatty acids having a stable phenyl ring. They are proven useful in many diseases, ranging from cancer, sickle cell anemia, ALS and Huntington's disease.

[0053] Phenylacetate is originally discovered as a plant hormone that regulates cell growth it has been studied in the past two decades as anti-cancer and cellular differentiating compounds. PA inhibits the growth of several cancer cell types of different lineages and, in some instances, it promotes their differentiation to a non-cancerous phenotype. Of interest are the effects of PA and PB on gliomas and neuroblastomas, originally thought to be mediated by inhibition of protein prenylation cholesterol and fatty acid biosynthesis. Subsequent studies have demonstrated that PA and PB inhibits the growth of several neoplastic cell types including breast cancer (Liu *et al.*, 2007, *Cancer Chemother. Pharmacol.* 59, 217-225), prostate cancer, colon cancer and thyroid carcinoma. Furthermore, PA and PB can potentiate the action of other hormones such as estrogens and retinoids in regulating cancer cell growth. These anti-cancer actions of PA and PB have prompted clinical trials especially that these compounds display little toxicity (Lin *et al.*, 2009, *Clin. Cancer Res.* 15, 6241-6249; Cudkowicz *et al.*, 2009, *Amyotroph. Lateral. Scler.* 10, 99-106). The overall picture that emerges is that PA and PB act as mild agents that synergize or cooperate with other bioactive agents, some of which may be endogenous. In fact, physiological or pharmacologic actions of PA and PB can act alone or in synergy with differentiating agents such as retinoid to down-regulate key cell-cycle genes as well as angiogenic and growth factors and that promote tumor cell growth. Studies regarding the molecular mechanisms of action of PA has shed light on two important pathways for its action: induction of histone acetylation which regulates chromatin structure and regulation of steroid / nuclear receptor gene expression. In fact, PA and PB can bind and activate the Peroxisome Proliferator-activiated Receptor γ (PPAR) which belongs to the steroid

receptor superfamily of ligand-activated transcription factors (Samid *et al.*, 2000, *Clin. Cancer Res.* 6, 933-941). The latter finding would suggest that these compounds act similar to steroidal hormonal drugs and would explain the pleotropic action of PA and PB compounds in different diseases and different physiological settings to regulate metabolism, inflammation, cancer growth and cell differentiation.

[0054] Thus, although camel urine has been known for its healing properties in the Arabic traditional medicine which is practiced even today in Saudi Arabia, the identification of its active molecules has not yet been reported.

[0055] There is also disclosed a method of preparing camel urine extracts. The extracts may be prepared through the fractionation of camel urine samples using techniques well known in the art. For example, the sample may be fractionated using exclusion chromatography techniques or any other method known in the art for the separation of molecules based on their size, shape, hydrophilicity, hydrophobicity, charge, polarity, or any other inherent physical characteristics which may be employed for the isolation (or exclusion) of molecules from the urine sample of interest. The preferred method for the preparation of extracts according to the present invention is by using size exclusion filtering membranes excluding a fraction of molecules having a molecular weight larger than a set weight (i.e. having a predetermined molecular weight cut-off). The urine samples are filtered with the filtering membrane to fractionate the sample in a filtrate comprising smaller molecules and a retentate of larger molecules. Suitable molecular weight for exclusion are from at least 100 kDa, or from at least 50, or from at least 30 kDa, or from at least 10 kDa, or from at least 3 kDa. The preferred molecular weight for exclusion (i.e. the preferred molecular weight cut-off) is from at least 10 kDa.

[0056] In embodiments, there is described an extract from camel urine which comprises an NMR spectrum as set forth in Fig. 1. The extract may be used for the preparation of medicaments and/or for the treatment of various

diseases such as cancer, including but not limited to breast cancer, prostate cancer, and thyroid cancer; metabolic diseases such as defects in the urea-cycle enzymes; multiple sclerosis, sickle cell anaemia, amyotrophic lateral sclerosis and Huntington's disease.

[0057] In embodiments, there is described an extract from camel urine which comprises a HPLC fractionation spectrum as set forth in Fig. 8A, and preferably comprising fraction C of said HPLC fractionation spectrum as set forth in Fig. 8A. The extract may be used for the preparation of medicaments and/or for the treatment of various diseases such as cancer, including but not limited to breast cancer, prostate cancer, and thyroid cancer; metabolic diseases such as defects in the urea-cycle enzymes; multiple sclerosis, sickle cell anaemia, amyotrophic lateral sclerosis and Huntington's disease.

[0058] In embodiments, there is described an extract from camel milk prepared according to the method described above. Desert Bedouins and even ordinary people living in Saudi Arabia today are also known to mix camel urine and milk to get therapeutic effects. We therefore examined whether camel milk contains any remarquable molecules. Indeed, the milk from adult camels contains significant amounts of benzoate (table 5) albeit in lower amounts than in camel urine. However, camel milk is devoid of phenyl acetate.

[0059] In use, the extracts of the present invention may be used alone, or combined to each other for any therapeutic use for which they may be useful. According to another embodiment, the extracts of the present invention may also be used in food composition, such as for example nutraceutical compositions. Nutraceuticals are food or food product that provides health and medical benefits, including the prevention and treatment of disease. Products according to the present invention may range from isolated nutrients, dietary supplements, prebiotic, specific diets and herbal product supplement, and processed foods such as cereals, soups, and beverages. The compositions of the present invention may also be used as a functional food, a food ingredient, a food additive, a natural food additive, a

non-food ingredient, a cosmeto-food, a pharmaceutical, and a food supplement."

[0060] The present invention will be more readily understood by referring to the following examples which are given to illustrate the invention rather than to limit its scope.

EXAMPLE 1

Animals

[0061] Urine are collected from 15 male and 5 female adult camels (*Camelus dromedarius*) raised in separate geographic areas in Saudi Arabia, Jordan, Egypt, and Bahrain. In addition, urines are obtained from 2 adult dromedaries, 2 alpaca, and one llama and two elephants from a zoo near Montreal, Canada. Furthermore, urines are obtained from two adult male Sprague-Dawley laboratory rats. The urine samples are transported to the laboratory either on ice or after freezing.

EXAMPLE 2

NMR Spectroscopy

[0062] A urine sample (0.5 ml) is centrifuge-filtered at 12,000 g and 4°C for 15 minutes by using 10 kDa centrifugal filter tubes (Millipore, Billerica, MA, USA) to remove molecules and particles in the sample that have molecular weights of at least 10 kDa. The centrifugal filters are washed several times with 0.5 ml water, then centrifuged at 12000 x g at 4°C to remove glycerol from the filter membrane until no NMR signal is observed in the filtrate. Four hundred microliters of the filtrate are transferred to a 5 mm NMR tube and 100 µl of D_2O (Cambridge Isotope Laboratories, Inc.) are added to the NMR tube.

[0063] The NMR spectra are obtained using a Varian Inova 600 MHz instrument (Palo Alto, California). All NMR experiments are obtained using a one-dimensional presaturation sequence with gradients pulse sequence (zgpr in the standard Bruker pulse sequence library). The 1H NMR spectra are recorded by collecting 64 and 128 free induction decays (FIDs) and digitized

into 64 K complex data points over a spectral width of 12 ppm. The recycle delay time is set to 5 sec and the receiver gain is kept at a constant value of 32. Before Fourier transform, the FID values are multiplied by an exponential function equivalent to 1.0 Hz line broadening factor. All spectra are then visually phased and adjusted manually where necessary.

EXAMPLE 3

Identification of urine compounds using NMR spectroscopy

[0064] Select spectra are examined using the Chenomx NMR Suite (Chenomx Inc., Edmonton, Alberta, Canada). The metabolites' signals are examined and the assignments are made by fitting and comparing of the experimental spectra with reference spectra from the database using the Chenomx NMR Profiler software.

EXAMPLE 4

Identification of phenylacetate and benzoate in camel urine using Mass Spectrometry

[0065] Target chemicals are determined using an Agilent 7890 A GC (or equivalent) with 5975C MSD equipped with an Agilent 7683B automatic liquid sampler and an HP-5MS GC (or equivalent) column (30 m, 0.25mm i.d., 0.25 µm film thickness). Helium is used as the carrier gas, with a column flow rate of 1.0 ml/min in constant flow mode. Injector temperature is 280°C. The GC–MSD interface quadruple and the ion source temperatures are set at 280, 170 and 230°C, respectively. The GC oven temperature is kept at 50°C for 0.5 min, followed by the first ramp at 5°C / min to 225°C, second ramp at 3°C / min to 280°C, and holding for 1 min. Prior to quantification process, mass spectra and GC retention times of each compound from *m/z* 50 to 550 are obtained in full scan mode. The mass spectrometer used is operating in electron impact with an ionization voltage of 70 EV. The sample is injected in pulsed splitless mode.

[0066] The demonstration of BNZ and PAA in camel urine are independently confirmed by three laboratories using Gas Chromatography-

Mass Spectrometry (*GC-MS*) (Fig. 2). The MS at the top of each peak is searched using NIST (National Institute of Standards and Technology, an agency of the U.S. Commerce Department) library with the best fit. Usually the best-matched 25 compounds are displayed. The mass spectrum of benzoic acid on EI ionization shows molecular ions $C_7H_6O_2^{\bullet+}$ at m/z= 122. Their intensity is 95% of the base peak, which is characterized by $C_6H_5CO^+$ benzoyl ions at m/z=105. Other prominent fragments are $C_6H_5^+$ ions are at m/z=77 (90%) and $C_4H_3^+$ ions at m/z=51 (70%). The mass spectrum of phenylacetic acid on EI ionization shows molecular ions $C_8H_8O_2^+$ at m/z=136. Their intensity is 30% of the base peak, which is characterized by $C_6H_5CH_2^+$ ions at m/z=91.

EXAMPLE 5

Identification of other components of camel urine using Mass Spectrometry

Table 2. Organic Acids and Metabolites in Urine

#	Acid	Camel 1 µmol/mmol creatinine	Camel 2 µmol/mmol creatinine
1	Benzoic	794	1374
2	Butyrylglycinic	2	3
3	Citric	2	11
4	Ethylmalonic	1	3
5	Glutaric	0	2
6	Glyceric	2	6
7	Glycolic	2	8
8	Hexanoylglycenic	1	1
9	Hippuric	91	6436
10	Homogentisic	0	1
11	Homovanillic	1	1
13	Isobutyrylglycinic	6	6
14	Isovalerylglycinic	4	3
15	Lactic	53	101
16	Malonic	1	0
17	Methylcitric	2	7
18	Methylmalonic	0	5
19	Methylsuccinic	5	12
20	N-acetylaspartic	1	0
21	Oxalic	55	159
22	Oxoprolinic (pyroglutamic)	6	3
23	Phenylpropionylglycinic	0	2
24	Phenylacetic	85	28
25	Phenyllactic	0	1
26	Proprionylglycinic	0	2
27	Pyruvic	1	1
28	Sebacic	1	3
29	Suberic	1	3
30	2-hydroxyadipic	1	1
31	2-hydroxyglutaric	1	2
32	2-hydroxyisovaleric	2	1
33	2-hydroxyphenylacetic	1	2
34	2-methyl-3-hydroxybutiric	8	11
35	2-methylacetoacetique	1	3
36	2-methylbutyrylglycinic	2	1
37	3-hydroxybutyric	0	3
38	3-hydroxyisovaleric	19	37
39	3-hydroxy-3-methylglutaric	26	49
40	3-hydroxypropionic	7	32
41	3-methylcrotonylglycinic	1	0
42	3-methylglutaconic	3	4
43	4-hydroxyphenylacetic	83	45
44	4-hydroxyphenyllactic	7	10

[0067] Urine samples from 2 camels are subjected to mass spectrometry as described above in Example 4.

EXAMPLE 6

Identification of other components of camel urine using Mass Spectrometry compared to human urine

Table 3. Organic Acids and Metabolites in Urine

Metabolite name (acid)	Camel		Human	
	Average	SEM	Average	SEM
ACETOACETIC	0.00	0.00	1.55	0.19
ADIPIC	1.33	0.22	1.00	0.08
BENZOIC	1484.00	124.82	2.45	0.14
BUTYRYLGLYCINE	1.67	0.22	0.00	0.00
CITRIC	4.33	0.88	310.82	19.16
ETHYLMALONIC	2.00	0.17	2.82	0.19
FUMARIC	0.33	0.08	0.55	0.06
GLUTARIC	0.67	0.17	0.45	0.05
GLYCERIC	4.33	0.36	4.00	0.46
GLYCOLIC	6.00	0.54	43.73	1.64
HEXANOYLGLYCINE	0.67	0.08	0.00	0.00
HIPPURIC	2897.67	458.52	251.73	24.35
HOMOGENTISIC	0.67	0.08	0.00	0.00
HOMOVANILLIC (HVA)	1.33	0.11	2.00	0.07
ISOBUTYRYLGLYCINE	5.00	0.38	0.27	0.03
ISOVALERYLGLYCINE	3.00	0.23	0.73	0.08
LACTIC	60.67	5.65	22.45	2.12
MALONIC	0.33	0.08	0.09	0.02
METHYLCITRIC	4.00	0.39	1.36	0.05
METHYLMALONIC	3.00	0.38	0.91	0.02
METHYLSUCCINIC	9.33	0.73	0.91	0.05
MEVALONOLACTONE	0.00	0.00	0.18	0.04
N-ACETYLASPARTIC	0.33	0.08	4.36	0.17
OXALIC	102.00	8.66	22.27	0.63
OXOPROLINE(PYROGLUTAMIC)	3.67	0.33	27.36	1.08
PHENYLPROPIONYLGLYCINE	0.67	0.17	0.00	0.00
PHENYLACETIC	53.33	4.64	0.00	0.00
PHENYLLACTIC	0.33	0.08	0.00	0.00
PHENYLPYRUVIC	0.00	0.00	0.00	0.00
PROPIONYLGLYCINE	0.67	0.17	0.09	0.02
PYRUVIC	1.00	0.09	11.55	1.28
SEBACIC	2.00	0.17	0.00	0.00
SUBERIC	2.67	0.24	1.09	0.12
SUCCINYLACETONE	0.00	0.00	0.00	0.00
VANILLYMANDELIC(VMA)	0.00	0.00	1.36	0.07
2-HYDROXYADIPIC	1.00	0.09	0.00	0.00
2-HYDROXYGLUTARIC	1.33	0.11	3.18	0.18
2-HYDROXYISOCAPROIC	0.00	0.00	0.00	0.00
2-HYDROXYISOVALERIC	1.00	0.14	0.09	0.02
2-HYDROXYPHENYLACETIC	1.67	0.13	0.45	0.07
2-METHYL-3-HYDROXYBUTYRIC	8.67	0.66	2.55	0.09
2-METHYLACETOACETIC	2.33	0.19	1.91	0.06

Table 3. Organic Acids and Metabolites in Urine (continued)

2-MÉTHYLBUTYRYLGLYCINE	1.00	0.14	0.00	0.00
2-OXOADIPIC	0.00	0.00	0.55	0.05
2-OXOGLUTARIC	0.00	0.00	19.09	1.58
2-OXOISOVALERIC	0.00	0.00	0.73	0.17
3-HYDROXYBUTYRIC	1.67	0.22	1.00	0.05
3-HYDROXYGLUTARIC	0.00	0.00	0.64	0.05
3-HYDROXYISOVALERIC	30.33	2.30	22.00	0.86
3-HYDROXY-3-METHYLGLUTARIC	61.67	6.35	23.91	0.96
3-HYDROXYPROPIONIC	20.00	1.89	20.27	1.02
3-METHYLCROTONYLGLYCINE	0.33	0.08	0.18	0.04
3-METHYLGLUTACONIC	5.00	0.43	2.55	0.12
3-METHYLGLUTARIC	0.00	0.00	0.09	0.02
4-HYDROXYBUTYRIC	0.00	0.00	0.00	0.00
4-HYDROXYPHENYLACETIC	52.67	4.48	11.55	0.49
4-HYDROXYPHENYLLACTIC	7.33	0.56	0.36	0.04
4-HYDROXYPHENYLPYRUVIC	0.00	0.00	2.00	0.10

* Values are in µmol/mmol of creatinine, Number of subjects: Camel, N=3, Human, N=13

EXAMPLE 7

Comparison of four metabolites in the urine of animals related to camels using Mass Spectrometry

Table 4. Concentratration of Benzoate, Phenylacetate, Hippurate and Citrate in urine of animals related to camel

	Benzoate	Phenylacetate	Hippurate	Citrate
Elephant	9	2	9836	UD
Dromedary 1	3	UD	7285	UD
Dromedary 2	6	UD	5790	3
Alpaca 1	6	1	5977	UD
Alpaca 2	3	3	7381	UD
Llama	8	UD	9515	6
Rat	2	1	507	1833

Note:*UD: means undetectable.

[0068] Concentrations of four relevant metabolites in the urine of animals raised in the zoo. The alpaca and llama are species related to the

camel. Rats were raised in a laboratory. A total of 57 metabolites are assayed but this table shows only 4. Values are expressed in µmol/mmol of creatinine.

EXAMPLE 8

Fractionation of camel urine using reversed phase-HPLC

[0069] Adult male camel urine previously lyophilized is reconstituted with an equivalent amount of 0.1 % trifluoroacetic acid (TFA) in water, then placed on ice and processed for HPLC within two hours. 10 to 100 microliters of this reconstituted urine solution is injected into either a Waters™ HPLC apparatus or an equivalent Beckman "Gold"™ HPLC apparatus. Both apparatuses are fitted with a 300 mm C-18™ column. Elution from the column is done using an increasing linear isocratic gradient of acetonitrile in water containing 0.1 % TFA. The gradient is increased from 5% to 75% acetonitrile. The absorbancy is monitored at 220 nm wavelength during the elution and fractions are collected manually into plastic tubes. After collection, the fractions are promptly placed in a Savant™ Speed-vac apparatus in order to dry the samples. Now referring to Fig. 4A, the gradient is shown with the x-axis indicating time, in minutes. The absorbency at 220 nm is recorded on the y-axis.

EXAMPLE 9

Bioassay of the collected fractions following HPLC separation

[0070] The fractions (peaks) indicated by arrows on Fig. 4B. are lyophilized and each is reconstituted in one (1) ml of RPMI culture medium (without serum) and tested for biological activity using MCF7 cells. The biological activity is tested in absence (Vehicle control, i.e. RPMI medium alone) or presence of 10 microliters of the reconstituted fractions. It can be seen from Fig. 4B that fraction C display an inhibitory activity.

EXAMPLE 10

Assessment of cell proliferation

[0071] The breast cancer cell line called MCF7 is obtained from the American Type Tissue Culture Collection. The KS cells are passaged and the culture medium is changed every other day in presence or in absence of any of the samples mentioned above for the indicated periods ranging from 24-96 hrs. ^{3}H-thymidine incorporation is measured as described (Guo WX et al., 1996, *Am J Pathol* 148: 1999-2008). In most experiments, data are reported as means ± SEM of sextuplet determinations. Statistical analysis is determined by student t-test.

EXAMPLE 11

Comparison of four metabolites in the milk of camels using Mass Spectrometry

Table 5. Concentrations of Benzoate, Phenylacetate, Hippurate and Citrate in the milk of 5 adult camels.

	Benzoate	Phenylacetate	Lactate	Citrate
Camel #EG2	20	UD	30	3326
Camel #EG3	23	UD	42	3091
Camel #EG4	11	UD	55	3087
Camel #EG5	38	UD	46	3461
Camel #EG6	17	UD	27	3455

Note:*UD: means undetectable.

[0072] Concentrations of four relevant metabolites in the milk of 5 adult camels. A total of 57 metabolites are assayed but this table shows only 4. Values are expressed in µmol/mmol of creatinine*

EXAMPLE 12

Identification of other components of camel milk using Mass Spectrometry

Table 6. Organic Acids and Metabolites in Milk

#	ACIDES	µmol/L
1	ACETOACETIQUE	1
2	ADIPIQUE	0
3	**BENZOIQUE**	38
4	BUTYRYLGLYCINE	0
5	CITRIQUE	3461
6	ETHYLMALONIQUE	0
7	FUMARIQUE	1
8	GLUTARIQUE	0
9	GLYCERIQUE	2
10	GLYCOLIQUE	0
11	HEXANOYLGLYCINE	0
12	HIPPURIQUE	0
13	HOMOGENTISIQUE	0
14	HOMOVANILLIQUE (HVA)	1
15	ISOBUTYRYLGLYCINE	0
16	ISOVALERYLGLYCINE	0
17	LACTIQUE	46
18	MALONIQUE	0
19	METHYLCITRIQUE	0
20	METHYLMALONIQUE	0
21	METHYLSUCCINIQUE	0
22	MEVALONOLACTONE	0
23	N-ACETYLASPARTIQUE	0
24	OXALIQUE	9
25	OXOPROLINE(PYROGLUTAMIQUE)	4
26	PHENYLPROPIONYLGLYCINE	0
27	PHENYLACETIQUE	0
28	PHENYLLACTIQUE	0
29	PHENYLPYRUVIQUE	18
30	PROPIONYLGLYCINE	1
31	PYRUVIQUE	10
32	SEBACIQUE	0
33	SUBERIQUE	0
34	SUCCINYLACETONE	0
35	VANILLYMANDELIQUE (VMA)	0
36	2-HYDROXYADIPIQUE	0
37	2-HYDROXYGLUTARIQUE	1
38	2-HYDROXYISOCAPROIQUE	0
39	2-HYDROXYISOVALÉRIQUE	0
40	2-HYDROXYPHENYLACETIQUE	0
41	2-METHYL-3-HYDROXYBUTYRIQUE	0
42	2-METHYLACETOACETIQUE *	0
43	2-MÉTHYLBUTYRYLGLYCINE	0
44	2-OXOADIPIQUE	7
45	2-OXOGLUTARIQUE	15
46	2-OXOISOVALERIQUE	0
47	3-HYDROXYBUTYRIQUE	1
48	3-HYDROXYGLUTARIQUE	0
49	3-HYDROXYISOVALERIQUE	0
50	3-HYDROXY-3-METHYLGLUTARIQUE	0
51	3-HYDROXYPROPIONIQUE	33
52	3-METHYLCROTONYLGLYCINE	0
53	3-METHYLGLUTACONIQUE	0
54	3-METHYLGLUTARIQUE	0
55	4-HYDROXYBUTYRIQUE	0
56	4-HYDROXYPHENYLACETIQUE	0
57	4-HYDROXYPHENYLLACTIQUE	1
58	4-HYDROXYPHENYLPYRUVIQUE	26

EXAMPLE 13

Identification of components of rat urine using Mass Spectrometry

[0073] Urine from two adult male Sprague-Dawley laboratory rats is obtained and subjected to mass spectrometry as described above. The organic acid content is determined:

Table 7. Organic Acids in rat urine

#		Rat	
	Organic Acids	Rat 1	Rat 2
1	ACETOACETIC	3	3
2	ADIPIC	7	6
3	BENZOIC	2	2
4	BUTYRYLGLYCINE	5	5
5	CITRIC	1845	1821
6	ETHYLMALONIC	23	21
7	FUMARIC	7	7
8	GLUTARIC	4	5
9	GLYCERIC	601	583
10	GLYCOLIC	30	32
11	HEXANOYLGLYCINE	0	0
12	HIPPURIC	496	518
13	HOMOGENTISIC	1	1
14	HOMOVANILLIC (HVA)	2	2
15	ISOBUTYRYLGLYCINE	1	1
16	ISOVALERYLGLYCINE	3	3
17	LACTIC	848	930
18	MALONIC	0	0
19	METHYLCITRIC	2	2
20	METHYLMALONIC	6	6
21	METHYLSUCCINIC	8	8
22	MEVALONOLACTONE	0	0
23	N-ACETYLASPARTIC	3	3
24	OXALIC	78	75
25	OXOPROLINE(PYROGLUTAMIC)	82	77
26	PHENYLPROPIONYLGLYCINE	0	0
27	PHENYLACETIC	1	1
28	PHENYLLACTIC	1	1
29	PHENYLPYRUVIC	0	0
30	PROPIONYLGLYCINE	0	0
31	PYRUVIC	123	110
32	SEBACIC	1	1
33	SUBERIC	3	2
34	SUCCINYLACETONE	0	0
35	VANILLYMANDELIC (VMA)	0	0

Table 7. Organic Acids in rat urine (continued)

36	2-HYDROXYADIPIC	3	3
37	2-HYDROXYGLUTARIC	9	9
38	2-HYDROXYISOCAPROIC	0	0
39	2-HYDROXYISOVALÉRIC	0	0
40	2-HYDROXYPHENYLACETIC	0	1
41	2-METHYL-3-HYDROXYBUTYRIC	1	2
42	2-METHYLACETOACETIC *	4	10
43	2-MÉTHYLBUTYRYLGLYCINE	1	1
44	2-OXOADIPIC	9	7
45	2-OXOGLUTARIC	302	253
46	2-OXOISOVALERIC	0	0
47	3-HYDROXYBUTYRIC	13	15
48	3-HYDROXYGLUTARIC	0	0
49	3-HYDROXYISOVALERIC	4	4
50	3-HYDROXY-3-METHYLGLUTARIC	4	4
51	3-HYDROXYPROPIONIC	19	17
52	3-METHYLCROTONYLGLYCINE	0	0
53	3-METHYLGLUTACONIC	2	2
54	3-METHYLGLUTARIC	1	1
55	4-HYDROXYBUTYRIC	1	2
56	4-HYDROXYPHENYLACETIC	20	19
57	4-HYDROXYPHENYLLACTIC	9	9
58	4-HYDROXYPHENYLPYRUVIC	24	21

[0074] While preferred embodiments have been described above and illustrated in the accompanying drawings, it will be evident to those skilled in the art that modifications may be made without departing from this disclosure. Such modifications are considered as possible variants comprised in the scope of the disclosure.

CLAIMS:

1. An extract from camel urine comprising an NMR spectrum as set forth in figure 1.

2. An extract from camel urine comprising a HPLC fractionation spectrum as set forth in figure 8A.

3. The extract according to claim 2, wherein said extract comprises a fraction C of said HPLC fractionation spectrum as set forth in figure 8A.

4. An extract from camel milk comprising at least one compound chosen from benzoate, lactate and citrate.

5. The extract according to claim 4, further comprising at least one compound chosen from acetoacetic acid, fumaric acid, glyceric acid, homovanillic acid, oxalic acid, oxoprolic acid, phenylpyruvic acid, propionylglycinic acid, pyruvic acid, 2-hydroxyglutaric acid, 2-oxoadipic acid, 2-oxoglutaric, 3-hydroxybutiric acid, 3 hydroxypropionic acid, 4-hydroxyphenyllactic acid, and 4-hydroxyphenylpyruvic acid.

6. A pharmaceutical composition comprising:
   - an extract from camel according to any one of claims 1 to 5, or combinations thereof; and
   - a pharmaceutically acceptable carrier.

7. A pharmaceutical composition comprising:
   - at least one compound as identified by a peak of an NMR spectrum as defined in figure 1, a HPLC fractionation spectrum as set forth in figure 8A or a fraction C thereof; and
   - a pharmaceutically acceptable carrier.

8. The use of an extract from camel according to any one of claims 1 to 5, or combination thereof, for the preparation of a medicament for the treatment of a disease.

9. The use of an extract from camel according to any one of claims 1 to 5, or combination thereof, for the treatment of a disease.

10. The use of at least one compound as identified by a peak of an NMR spectrum as set forth in figure 1, a HPLC fractionation spectrum as set forth in figure 8A or a fraction C thereof for the preparation of a medicament for the treatment of a disease.

11. The use of at least one compound as identified by a peak of an NMR spectrum as set forth in figure 1, a HPLC fractionation spectrum as set forth in figure 8A, or a fraction C thereof for the treatment of a disease.

12. The use according to any one of claims 10 - 11, wherein said at least one compound is benzoate, phenylacetate or a combination thereof.

13. The use according to any one of claims 10 - 11, wherein said at least one compound is chosen from Butyrylglycinic acid, Citric acid, Ethylmalonic acid, Glyceric acid, Glycolic acid, Glutaric acid, Hexanoylglycenic acid, Hippuric acid, Homovanillic acid Homogentisic acid, Isobutyrylglycinic acid, Isovalerylglycinic acid, Lactic acid, Malonic acid, Methylcitric acid, Methylmalonic acid, Methylsuccinic acid, N-acetylaspartic acid, Oxalic acid, Oxoprolinic (pyroglutamic) acid, Phenylpropioniglycinic acid, Phenyllactic, Propionylglycinic acid, Pyruvic acid, Sebacic acid, Suberic acid, 2-hydroxyadipic acid, 2-hydroxyglutaric acid, 2-hydroxyisovaleric acid, 2-hydroxyphenylacetic acid, 2-methyl-3-hydroxybutiric acid, 2-methylacetoacetique acid, 2-methylbutyrylglycinic acid, 3-hydroxyisovaleric acid, 3-hydroxy-3-methylglutaric acid, 3-hydroxybutyric acid, 3-hydroxypropionic acid, 3-methylcrotonylglycinic acid, 3-methylglutaconic acid,

4-hydroxyphenylacetic acid, 4-hydroxyphenyllactic acid, retinoic acid derivatives.

14. The use according to any one of claims 8 - 13, wherein said disease is chosen from a cancer, a neoplasm, a multidrug resistant tumor, and a haematological malignancy.

15. The use according to claim 14, wherein said cancer is chosen from a breast cancer,a colon cancer, a prostate cancer, a malignant glyoma, and a thyroid cancer.

16. The use according to any one of claims 8 - 11 and 13, wherein said disease is a metabolic defect in a urea-cycle enzyme.

17. The use according to any one of claims 8 - 13, wherein said disease is chosen from multiple sclerosis, sickle cell anaemia, amyotrophic lateral sclerosis, and Huntington's disease.

18. A method of treating a disease in a subject in need thereof, the method comprising administering to said subject a therapeutically effective amount of of an extract from camel according to any one of claims 1 to 5 or combination thereof.

19. A method of treating a disease in a subject in need thereof, the method comprising administering to said subject a therapeutically effective amount of at least one compound as identified by a peak of an NMR spectrum as set forth in figure 1, an HPLC fractionation spectrum as set forth in figure 8A or a fraction C thereof.

20. The method according to claim 19, wherein said at least one compound is benzoate, phenylacetate or a combination thereof.

21. The method according to claim 19, wherein said at least one compound is chosen from Butyrylglycinic acid, Citric acid, Ethylmalonic acid, Glyceric acid, Glycolic acid, Glutaric acid, Hexanoylglycenic acid, Hippuric acid, Homovanillic acid Homogentisic acid, Isobutyrylglycinic acid, Isovalerylglycinic acid, Lactic acid, Malonic acid, Methylcitric acid, Methylmalonic acid, Methylsuccinic acid, N-acetylaspartic acid, Oxalic acid, Oxoprolinic (pyroglutamic) acid, Phenylpropioniglycinic acid, Phenyllactic, Propionylglycinic acid, Pyruvic acid, Sebacic acid, Suberic acid, 2-hydroxyadipic acid, 2-hydroxyglutaric acid, 2-hydroxyisovaleric acid, 2-hydroxyphenylacetic acid, 2-methyl-3-hydroxybutiric acid, 2-methylacetoacetique acid, 2-methylbutyrylglycinic acid, 3-hydroxyisovaleric acid, 3-hydroxy-3-methylglutaric acid, 3-hydroxybutyric acid, 3-hydroxypropionic acid, 3-methylcrotonylglycinic acid, 3-methylglutaconic acid, 4-hydroxyphenylacetic acid, 4-hydroxyphenyllactic acid.

22. The method according to any one of claims 18 - 21, wherein said disease is chosen from a cancer, a neoplasm, a multidrug resistant tumor, and a haematological malignancy.

23. The method according to claim 22, wherein said cancer is chosen from a breast cancer, a colon cancer, a prostate cancer, a malignant glyoma and a thyroid cancer,

24. The method according to any one of claims 18 - 19 and 21, wherein said disease is a metabolic defect in a urea-cycle enzyme.

25. The method according to any one of claims 18 - 21, wherein said disease is chosen from multiple sclerosis, sickle cell anemia, amyotrophic lateral sclerosis, and Huntington's disease.

26. A method of producing an extract from camel urine having an NMR spectrum as set forth in figure 1 comprising:

- removing a fraction of at least 10 kDa from a camel urine sample to produce an extract having at least one molecule of molecular weight lower than 10 kDa.

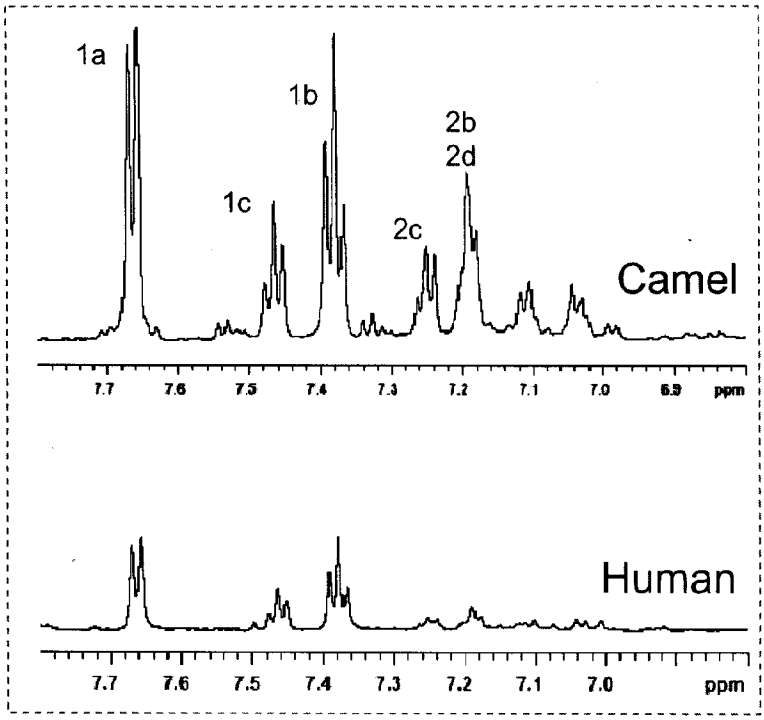
27. The method according to claim 26, wherein said removing is by filtration of said camel urine sample.

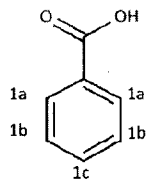
28. The method according to claim 27, wherein said filtration is performed with a filter membrane.

29. The method according to claim 28, wherein said filter membrane has pores preventing passage of molecules having at least 10 kDa.

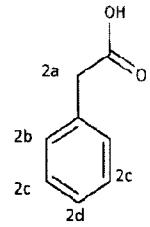
30. The method according to any one of claims 28 - 29, wherein said filter membrane is treated with water prior to filtration of said camel urine sample.

Fig. 1A





Benzoate



Phenylacetate

Fig. 1B

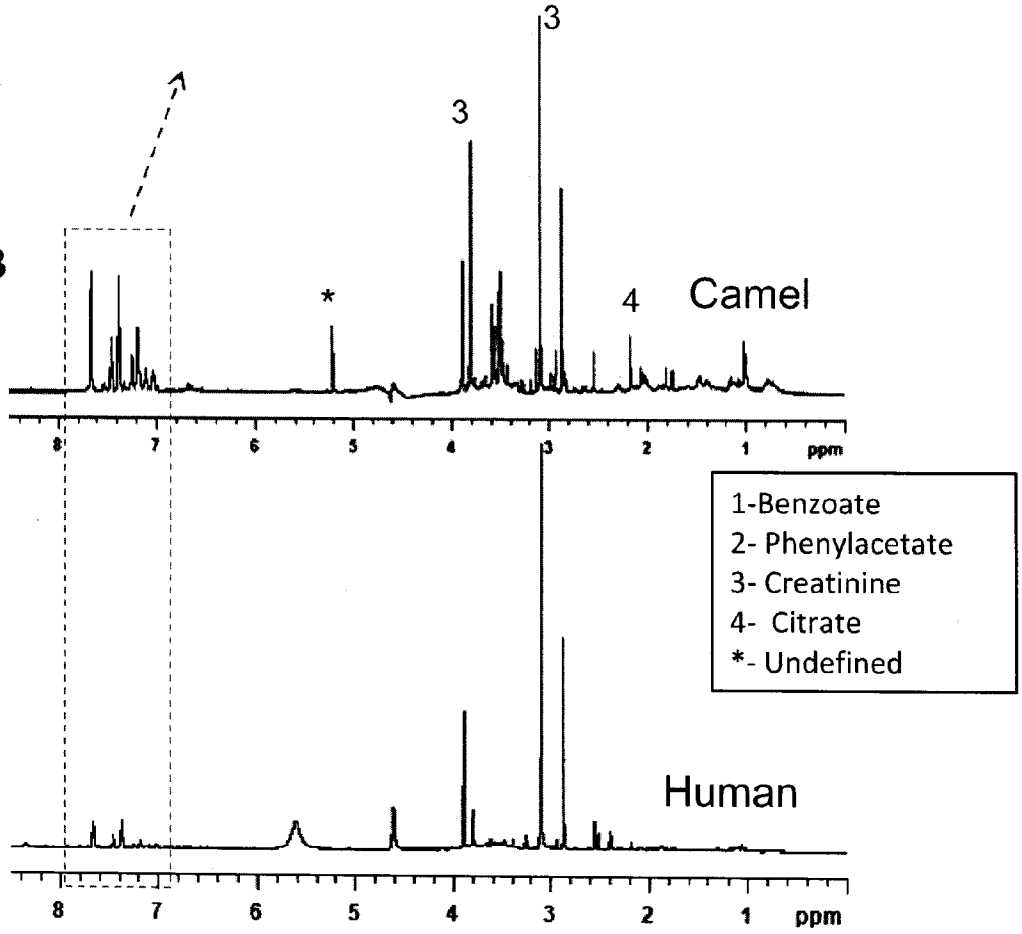


Fig 2A

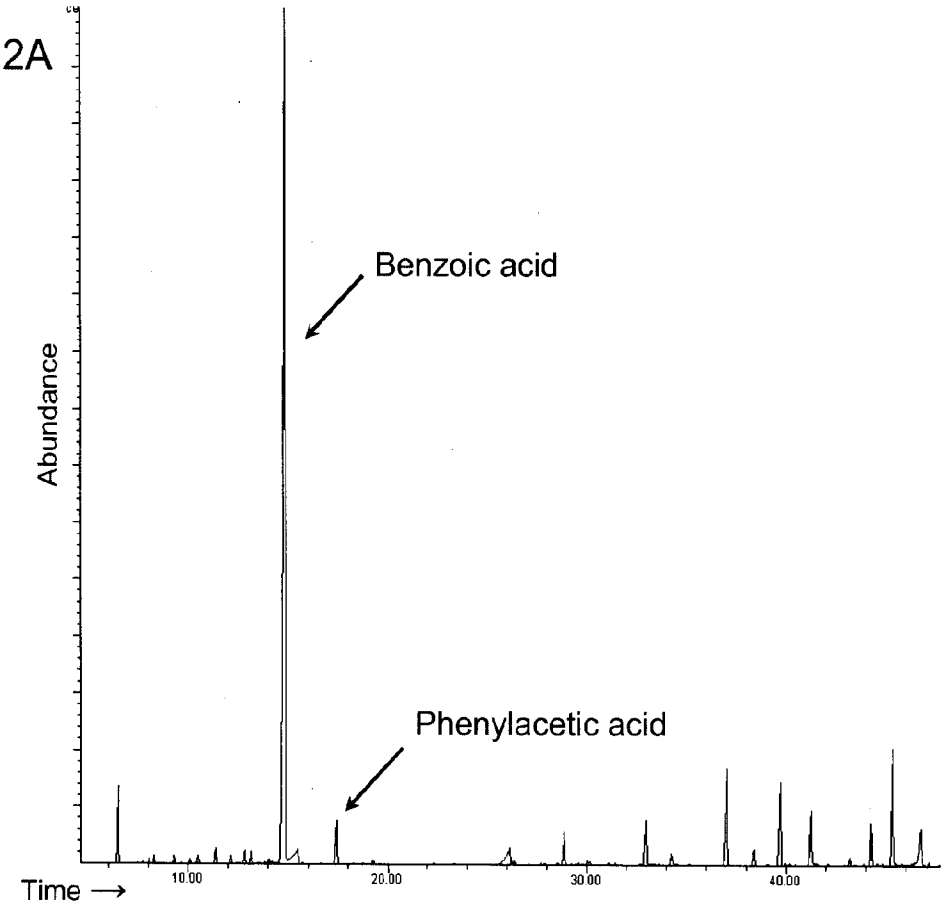
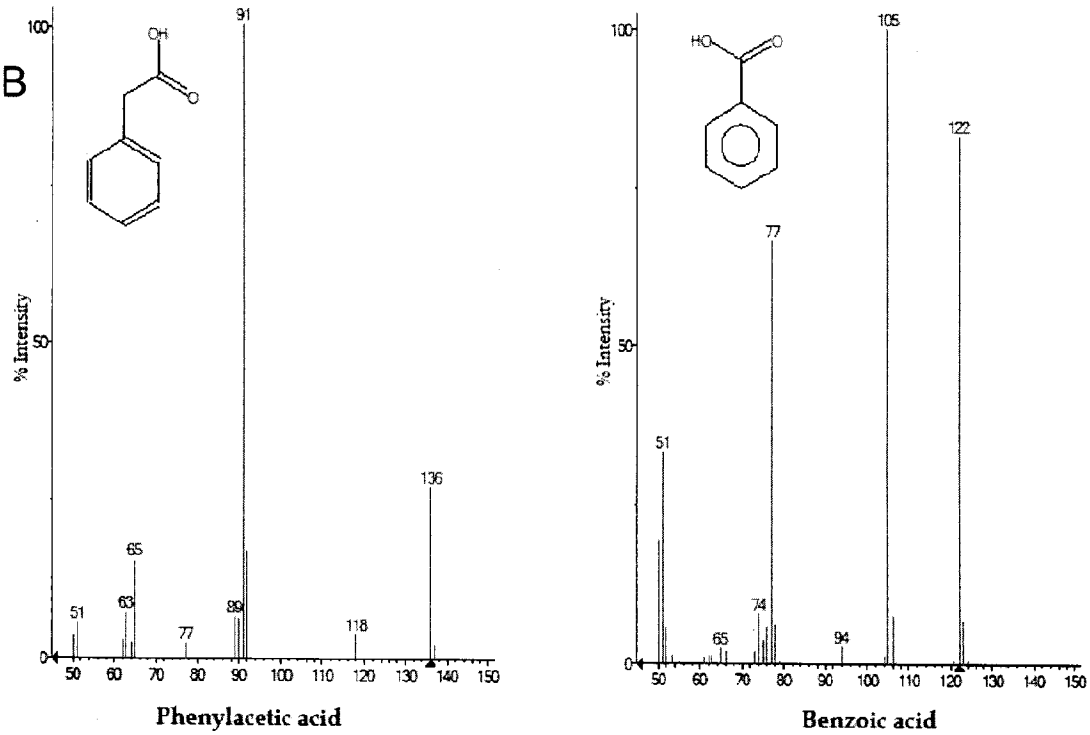

Benzoic acid
Phenylacetic acid
Abundance
Time
10.00
20.00
30.00
40.00

Fig 2B


% Intensity
91
136
65
63
51
89
77
118
Phenylacetic acid
% Intensity
105
122
77
51
74
65
94
Benzoic acid

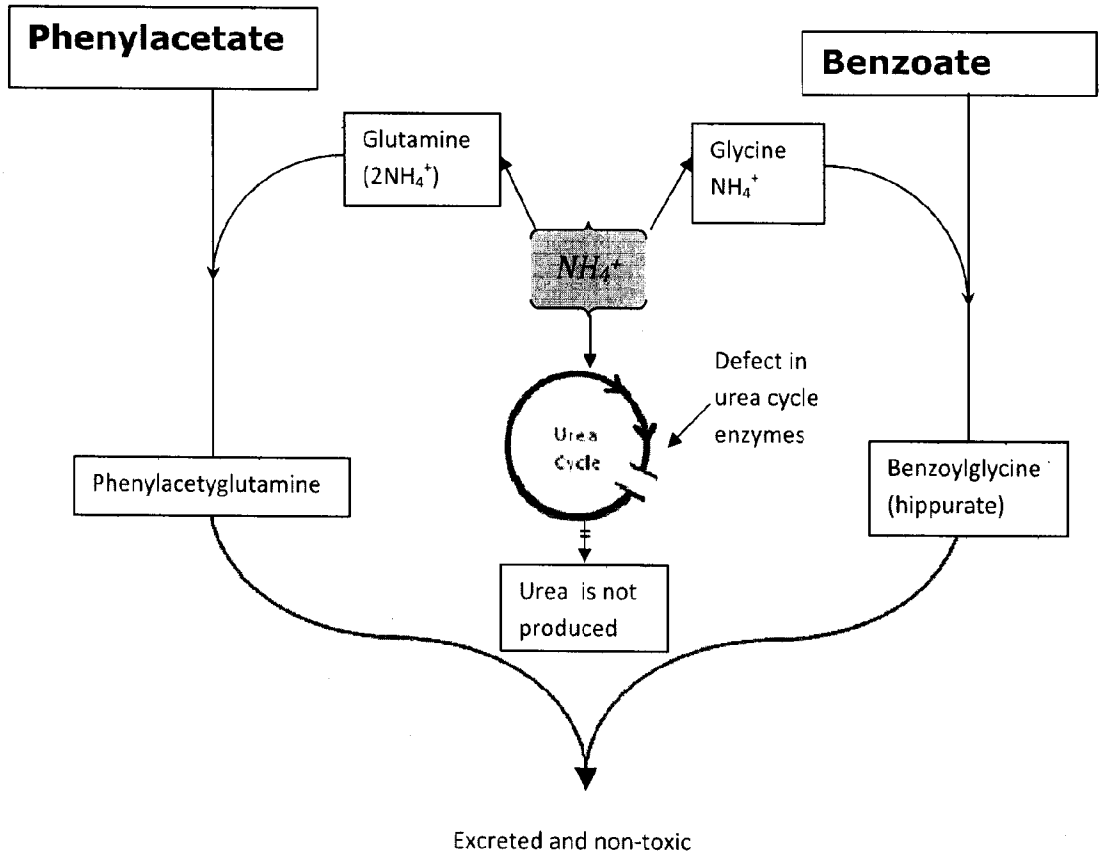
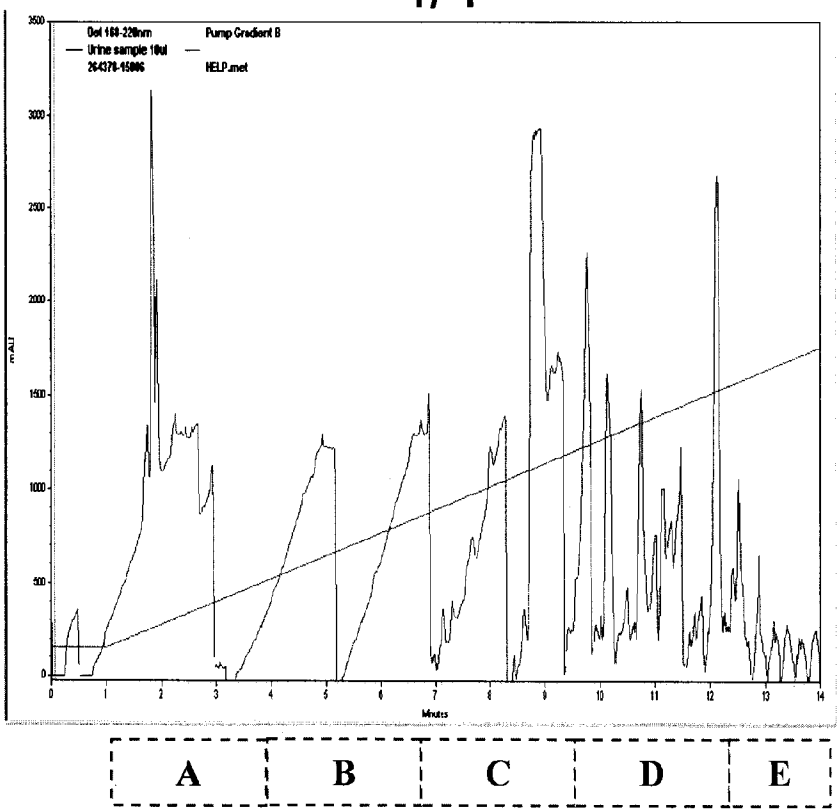
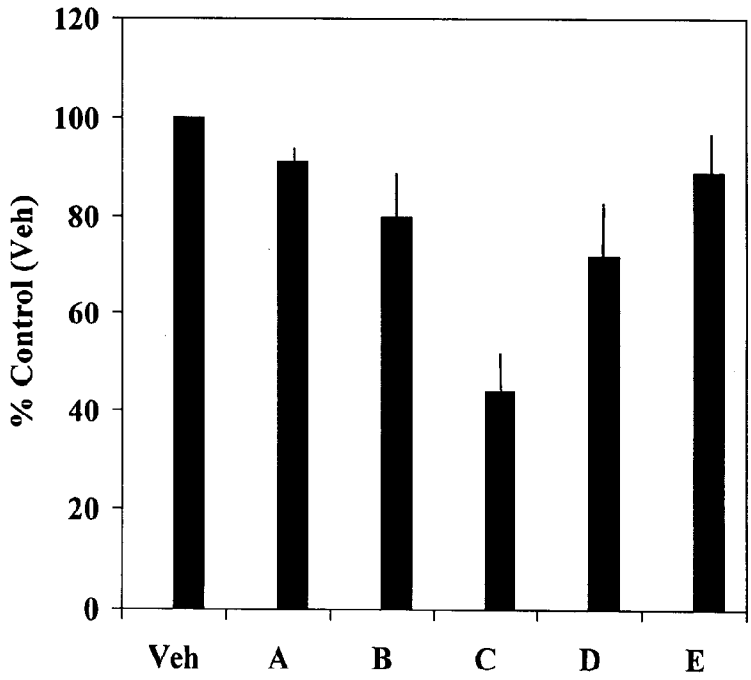

Phenylacetate
Benzoate
Glutamine
(2NH4+)
Glycine
NH4+
NH4+
Defect in
urea cycle
enzymes
Urea
Cycle
Phenylacetyglutamine
Benzoylglycine
(hippurate)
Urea is not
produced
Excreted and non-toxic

Fig. 3


Pump Gradient B
HELP.met
mAU
Minutes
A
B
C
D
E

4A


% Control (Veh)
120
100
80
60
40
20
0
Veh
A
B
C
D
E

4B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2011/000953

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61K 31/19*** (2006.01) , ***A61K 35/20*** (2006.01) , ***A61K 35/22*** (2006.01) , *B01D 61/14* (2006.01) , *B01D 61/24* (2006.01)

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)

IPC: A61K 31/19 (2006.01) , ***A61K 35/20*** (2006.01) , ***A61K 35/22*** (2006.01) , *B01D 61/14* (2006.01) , *B01D 61/24* (2006.01)

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

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

Canadian Patent database, United States Patent database, EPOQUE (Epodoc, English Ful-Text), PubMed, Scopus, Google (Keywords: camel, urine, milk, extract, benzoate, lactate, citrate, phenylacetate, cancer, multiple sclerosis, ALS, and related terms)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SULIMAN "Traditional medicine: The treatment of navus infection in a baby using the blood contents of an engorged camel tick in Shendi area" *Sudanese Journal of Public Health*, July 2010, 5(3), 164-165. (see entire document)	4-6, 8-17 and 26-30
X	YAGIL "Camels and camel milk" *FAO Animal Production and Health Paper*, 1982, Food and Agriculture Organization of the United Nations. (Obtained from http://www.fao.org/DOCREP/003/X6528E/X6528E00.htm) (see entire document)	4-6
X	AGRAWAL et al. "Beneficial effect of camel milk in diabetic nephropathy" *Acta Biomed.*, 2009, 80, 131-134. (see entire document)	4-6
X	MOHAMAD et al. "Camel milk as an adjuvant therapy for the treatment of type 1 diabetes: Verification of a traditional ethnomedical practice" *Journal of Medicinal Food*, 2009, 12(2), 461-465. (see entire document)	4-6

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 2011 (01-12-2011)	7 December 2011 (07-12-2011)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Wesley Sharman (819) 934-2326

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2011/000953

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] Claim Nos. : 18-25

because they relate to subject matter not required to be searched by this Authority, namely :

Although claims 18-25 are directed to methods of medical treatment of the human or animal body (Rule s39.1(iv) of the PCT), a search has been carried out on the alleged effects of the specific compounds defined in the present claims in treating disease.

2. [X] Claim Nos. : 1-30

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

(see extra sheet)

3. [ ] Claim Nos. :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

(see extra sheet)

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHABO et al. "Etiology of autism and camel milk as therapy" *Int. J. Dis. Human Dev.*, 2005, 4(2), 67-70. (see entire document)	4-6
X	WO2005023208 (KALEJAMN) 17 March 2005 (17-03-2005) (see entire document)	4-6
X	US20090297622 (KHORSHID) 3 December 2009 (03-12-2009) (see entire document)	8-17 and 26-30
X	KHORSID et al. "In vitro anticancer agent: I - Tissue culture of human lung cancer cells A549. II - Tissue culture study of mice leukemia cells L1210" *International Journal of Cancer Research*, 2006, 2(4), 330-344. (see entire document)	8-17 and 26-30
X	KHORSHID "Potential anticancer natural product against human lung cancer cells" *Trends in Medical Research*, 2009, 4(1), 8-15. (see entire document)	8-17 and 26-30
X	KHORSID et al. "Cytotoxic activity of bioactive fractions from PM 701" *Electronic Journal of Environmental, Agricultural and Food Chemistry*, 2009, 8(11), 1091-1098. (see entire document)	8-17 and 26-30
X	EL-SHAHAWY et al. "Spectral analysis, molecular orbital calculations and antimicrobial activity of PMF fraction extracted from PM-701" *International Journal of Pharma and Bio Sciences,* April-June 2010, 1(2), 1-20. (see entire document)	8-17 and 26-30
X	MOSHREF "PM701, a highly selective anticancerous agent against L1210 leukemia cells: In vivo clinical and histopathological study" *Journal of King Abdulaziz University - Medical Sciences*, 2007, 14(4), 85-99. (see entire document)	8-17 and 26-30
X	KABARITY et al. "Camel urine as a possible anticarcinogenic agent" *Arab Gulf J. Scient. Res. Agric. Biol. Sci.*, 1988, B6(1), 55-63. (see entire document)	8-17
X	ENNS et al. "Survival after treatment with phenylacetate and benzoate for urea-cycle disorders" *New England Journal of Medicine*, 2007, 356(22), 2282-2292. (see entire document)	8-17
X	BRACHMACHARI et al. "Sodium benzoate, a metabolite of cinnamon and a food additive, reduces microglial and astroglial inflammatory responses" *Journal of Immunology,* 2009, 183, 5917-5927. (see entire document)	8-17
X	LIU et al. "Modulation by phenylacetate of early estrogen-mediated events in MCF-7 breast cancer cells" *Cancer Chemother. Pharmacol.*, 2007, 59, 217-225. (see entire document)	8-17
X	WOODHOUSE "Chemotherapy investigations in cancer with reference to the influence of certain organic dibasic acids, diamino compounds and nitro compounds on tumors in mice" *Cancer Research*, 1947, 7, 398-401. (see entire document)	8-17
X	GB1200928 (FERLUX) 5 August 1970 (05-08-1970) (see entire document)	8-17
	LAVERMICOCCA et al. "Purification and characterization of novel antifungal compounds form the sourdough Lactobacillus plantarum strain 21B" *Applied and Environmental Microbiology*, 2000, 66(9), 4084-4090. (see entire document)	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2011/000953

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EVANS et al. "Retinoids: Present role and future potential" *British Journal of Cancer*, 1999, 80(1/2), 1-8. (see entire document)	8-17
X	LUPIEN et al. "Long-term treatment of homozygous familial hypercholesterolemia with 3-hydroxy-3-methylglutaric acid" *The Lancet*, 1978, 283-284. (see entire document)	8-17
X	LUPIEN et al. "Effects of 3-hydroxy-3-methylglutaric acid on plasma and low-density lipoprotein cholesterol levels in familial hypercholesterolemia" *Journal of Clinical Pharmacology*, 1979, 120-126. (see entire document)	8-17
X	PARK et al. "Pyruvate slows disease progression in a G93A SOD1 mutant transgenic mouse model" *Neuroscience Letters*, 2007, 413, 265-269. (see entire document)	8-17
X	DIEULEVEUX et al. "Antimicrobial spectrum and target site of D-3-phenyllactic acid" *International Journal of Food Microbiology*, 1998, 40, 177-183. (see entire document)	8-17
X	SHECHTER et al. "Hydrophenyl acetate derivatives inhibit protein tyrosine kinase activity and proliferation in Nb2 rat lymphoma cells and insulin-induced lipogenesis in rat adipocytes" *Molecular and Cellular Endocrinology*, 1991, 80, 183-192. (see entire document)	8-17
X	OHASHI et al. "The inhibitory effect of glycolic acid and lactic acid on melanin synthesis in melanoma cells" *Experimental Dermatology*, 2003, 12(S2) 43-50. (see entire document)	8-17
X	YANG et al. "Effects of glycolic acid on the induction of apoptosis via caspase-2 activation in human leukemia cell line (HL-60)" *Food and Chemical Toxicology*, 2004, 42, 1777-1784. (see entire document)	8-17
L	GARCIA RUIZ et la. "Cerebrospinal fluid homovanillic acid is reduced in untreated Huntington's disease" *Clinical Neuropharmacology*, 18(1), 58-63. (see entire document)	1-30
L	ROSA et al. "Inhibition of energy metabolism by 2-methylacetoacetate and 2-methyl-3-hydroxybutyrate in cerebral cortex of developing rats" *J. Inherit. Metab. Dis.*, 2005, 28, 501-515. (see entire document)	1-30
L	WATANABE et al. "Measurement of 3-hydroxyisovaleric acid in urine of biotin-deficient infants and mice by HPLC"*Journal of Nutrition*, 2005, 135(3), 615-618. (see entire document)	1-30

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2011/000953

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2005023208A1	17 March 2005 (17-03-2005)	AU2004270008A1	17 March 2005 (17-03-2005)
		AU2004270008B2	07 April 2011 (07-04-2011)
		CN1870972A	29 November 2006 (29-11-2006)
		EP1675565A1	05 July 2006 (05-07-2006)
		IL157814D0	28 March 2004 (28-03-2004)
		IL157814A	03 December 2007 (03-12-2007)
		US2007154443A1	05 July 2007 (05-07-2007)
		US7883691B2	08 February 2011 (08-02-2011)
US2009297622A1	03 December 2009 (03-12-2009)	None	
GB1200928A	05 August 1970 (05-08-1970)	BE709665A	19 July 1968 (19-07-1968)
		DE1617483A1	17 February 1972 (17-02-1972)
		FR6716M	17 February 1969 (17-02-1969)

Continuation of Box II:

Claims 1-30 of the current claims relate, at least in part, to extracts from camel urine, compositions comprising said extracts, use of said extracts, methods of using said extracts and methods of producing said extracts wherein the extracts are characterized by an NMR spectrum, an HPLC spectrum or a specific fraction of an HPLC spectrum. However, an NMR or HPLC spectrum cannot be viewed as fully and completely defining an extract, the components of an extract or their relative amounts. Along the same lines, claims 7, 10-17 and 19-25 of the current claims relate, at least in part, to compositions comprising compounds, uses of compounds and methods of using compounds wherein the compound is identified by a peak in an NMR spectrum, by a peak in HPLC spectrum or by a peak in a fraction of an HPLC spectrum. However, a compound cannot legitimately be identified by a single peak in an NMR spectrum or by a peak in an HPLC spectrum.

As a result, these claims fail to fully and completely define the extract or the compounds identified by a peak in an NMR or HPLC spectrum in any true or meaningful manner, causing the true scope of these claims to be indeterminable. Hence, these claims so lack clarity in view of Article 6 of the PCT and so lack support and disclosure in view of Article 5 of the PCT that a search over the entire scope of the present claims is not possible. Consequently, a search has only been carried out for those parts of the claims that have been fully and completely defined by the present claims and supported by the present description. This would include claims encompassing extracts that can be viewed as fully defined (such as those defined in claims 4 and 5) and compounds that are fully identified (such as those defined in claims 12, 13, 20 and 21).

Therefore, no search has been carried out for the subject matter of claims 1-3 and 7. Furthermore, the search carried out for claims 6, 8, 9 and 18 (and those claims dependent on these claims) only relates to their dependence on claims 4 and 5. No search has been carried out for the subject matter of claims 6, 8, 9 and 18 (and those dependent on these claims) when claims 6, 8, 9 and 18 are dependent on claims 1-3. Finally, any search carried out for the subject matter of claims 10, 11 and 19 (and those dependent on these claims) only relates to the use of compounds that are fully defined, namely those defined in claims 12, 13, 20 and 21.

Continuation of Box III:

The claims of the present application do not comply with the requirements of Rule 13 of the PCT. The present claims are not related to one invention or to a group of inventions that are so linked as to form a single general inventive concept.

The present claims are directed towards extracts from either camel urine or camel milk, compositions comprising said extracts, use of said extracts to treat disease, methods of using said extracts to treat disease and methods of producing said urine extracts. In addition, the present claims are directed towards compositions comprising compounds, uses of compounds and methods of using compounds wherein the compound is identified by a peak in an NMR spectrum, by a peak in HPLC spectrum or by a peak in a fraction of an HPLC spectrum wherein said spectra are those obtained for a camel urine extract.

These claims cannot be viewed as being linked by a single general **inventive** concept. The use of a bodily fluid of a camel (either urine or milk) to treat disease does not link the present claims since the use of camel urine and camel milk to treat disease is well-known (see for instance the teachings of the present description and D1-D13). Similarly, camel urine and camel milk extracts are known in the art (see for instance D6-D13) and such extracts cannot be viewed as inventive in light of the known use of camel urine and camel milk to treat disease. Therefore, the use of such extract also cannot act as a linking **inventive** feature. As a result, claims encompassing extracts from camel urine and claims encompassing extracts from camel milk cannot be viewed as linked by a single inventive concept.

In addition, claims encompasses specific compounds or combinations of specific compounds are also not linked by a single **inventive** concept. The compounds defined in present claims 4, 5, 12, 13, 20 and 21 are all known compounds. Their presence in camel milk or their identification in a camel urine does not link these compounds by a common **inventive** concept. This is particularly apparent since the compounds defined in claim 4 are known to be present in milk. In addition, the mere identification of a known compound in camel urine does not provide novelty to the compounds or to the known uses of these known compounds. As a result, since an extract as defined in claims 4 and 5 are viewed as a composition, each distinct composition, whether directed to a single compound or a combination of compounds (as encompasses by present claims 4 and 5 (i.e. "at least one compound" includes a combination of two or more compounds) represents a separate and distinct alleged invention. Furthermore, insofar as these compounds and combinations are known, their use in the treatment of each potential disease also represents a separate and distinct alleged invention. Thus, for example, extracts comprising benzoate represent a separate alleged invention compared to extracts comprising lactate or extracts comprising benzoate and pyruvic acid. In addition, the use of an extract comprising benzoate to treat breast cancer represents a separate alleged invention compared to the use of an extract comprising benzoate to treat multiple sclerosis or the use of an extract comprising benzoate and pyruvic acid to treat breast cancer.

Similarly, claims 12, 13, 20 and 21 all encompass the use (or method of using) of a single known compound or a combination of known compounds to treat disease. Since these compounds are all known, the treatment of each separate and distinct disease with each separate and distinct compound or combination of compounds represents its own separate and distinct allegedly inventive concept since each are directed to an allegedly new use of a known compound or a combination of known compounds. Thus, for example, the use of citric acid to treat thyroid cancer represents a separate alleged invention compared to the use of sebacic acid to treat thyroid cancer, the use of the combination of citric acid and sebacic acid to treat thyroid cancer, the use of citric acid to treat Huntington's disease or the use of citric acid and sebacic acid to treat Huntington's disease.

Claims 26-30 are directed to a general method of producing an extract from camel urine. Since extracts of camel urine are known (see D7-D13), this method also involves a separate and distinct allegedly inventive concept.