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Lipid profile of the ethanol - methanol (1:1) extracts of *Anacadium occidentale* and *Jatropha tanjorensis* administration in Wistar rats

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Abstract

Hyperlipidaemia is characterized by an increase in one or more of the plasma lipids. This study evaluated the lipid profile of albino Wistar rats administered ethanol-methanol extracts of *Anacadium occidentale* and *Jatropha tanjorensis* leaves. Twenty-five (25) male Wistar rats weighing between 180 - 220 g were divided into five (5) groups of five (5) rats each and treated thus: Group 1 (normal control received normal saline), group 2 and 3 administered low dose (400 mg/kg^{-1} b.wt.) and high dose (800 mg/kg^{-1} b.wt.) of *Anacadium occidentale* extract respectively, group 4 and 5 administered low dose (400 mg/kg^{-1} b.wt.) and high dose (800 mg/kg^{-1} b.wt.) of *Jatropha tanjorensis* extract respectively. At the end of the experiment, the rats were sacrificed to obtain the sera for the evaluation of serum lipid profile. The result revealed a significant (P<0.05) decrease in TC in all the groups except group IV compared with control. There was a significant (P<0.05) increase in TG and VLDL-c levels in all groups compared with control. HDL-c level significantly (P<0.05) increased in group III only compared with control. LDL-c level significantly (P<0.05) decreased in group III and V only compared with control. The LDL-c/HDL-c ratio showed no significant ($P\geq$0.05) difference between groups II, V and control, however group III significantly (P<0.05) decreased and group IV significantly (P<0.05) increased compared with the rest groups. The study suggests that the plant extracts possess lipid lowering potentials and may be employed in the treatment of metabolic disorders such as obesity and cardiovascular diseases.

Keywords: Hyperlipidaemia; Lipid profile; Metabolic disorders; *Anacadium occidentale; Jatropha tanjorensis*

1. Introduction

Cardiovascular disease (CVD) and related disorders remains the dominant cause of death both in men and women globally [1], and while it is recognized as a multifactorial disease with many risk factors, atherosclerosis is responsible for the major pathology contributing to end stage heart disease [2]. Hyperlipidaemia is considered one of the major risk factors causing cardiovascular diseases (CVDs). CVDs accounts for one third of total deaths around the world [3, 4]. Hyperlipidaemia is a medical condition characterized by an increase in one or more of the plasma lipids, including triglycerides, cholesterol, phospholipids and or plasma lipoproteins including very low-density lipoprotein and low-density lipoprotein along with reduced high-density lipoprotein levels [5]. This elevation of plasma lipids is among the leading risk factors associated with cardiovascular diseases. In the meantime, statins and fibrates remain the major anti-

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hyperlipidaemic agents for the treatment of elevated plasma cholesterol and triglycerides respectively, with severe side effects on the muscles and the liver [5]. It has been ranked as one of the greatest risk factors contributing to the prevalence and severity of coronary heart diseases. Coronary heart disease, stroke, atherosclerosis and hyperlipidaemia are the primary cause of death [6]. Hyperlipidaemia associated lipid disorders such as hypercholesterolemia and hypertriglyceridemia are considered to cause atherosclerotic cardiovascular disease [7]. The main aim of treatment in patients with hyperlipidaemia is to reduce the risk of developing ischemic heart disease or the occurrence of further cardiovascular disease or cerebrovascular disease [8]. Ineffectiveness and inability to afford synthetic drugs is a major constraint in management of hyperlipidaemia in developing countries such as Nigeria, so the search for naturally occurring locally available anti-hyperlipidaemic agent still continues.

Plants appear to be the major source of drugs for the majority of the world's population [9], with substances derived from higher plants constituting about a quarter of all prescribed medicines [10]. Several herbal medicines have advanced to clinical use in modern times [11]. It has been estimated that 25% of the modern medicines are made from plants first used traditionally. The reasons for this are complicated, probably from the ability of the plant to produce structurally diverse molecules, these molecules are made from renewable resource of raw by eco-friendly process [12]. Among several factors contributing towards the potential use of phytomedicine are safety, lack of adverse reactions and side effects which have been mostly found to particularly influence the use of such medicines in developed countries [13]. In rural areas, there are additional cultural factors that encourage the use of herbal preparations, people believe that where an area give rise to a particular disease it will also support plants that can be used to cure it, also hundreds of primary health care centres which are intended to serve rural areas which lack staff, diagnostic facilities and adequate supplies of medicines [14]. Although there is a growing popularity of herbal medicines as safe, scientists still advocate proper physiological and toxicological tests in order to ensure safety in the use of traditional medicines [15, 16].

Jatropha tanjorensis belongs to the family 'Euphorbiaceae' and is widely grown in southern Nigeria [17]. Its leaf is commonly consumed as vegetable in many parts of southern Nigeria. It is commonly called 'hospital too far' (Pidgin English), 'lapalapa' or 'Iyana-Ipaja' (Yoruba), 'Ugu-Oyibo' (Igbo) [18]. It is called 'Catholic vegetable or Reverend father's vegetable [19], possibly because it is grown in the premises of the catholic churches as ornamentals. *Jatropha tanjorensis* has been used locally as a source of leafy vegetable and as medicinal plant for a number of years. A study by Olayiwola *et al*., showed that *Jatropha tanjorensis* is popular as a natural remedy against diabetes in southern Nigeria [20]. *Jatropha tanjorensis* has also been showed to exhibit antibacterial activity [18]. It is also used ethnomedically in the treatment of hypertension [19]. The leaf extract also has antioxidant property and is effective in the treatment of malaria in southern Nigeria [21]. Extracts from the plant leaves have also been used in Nigeria to control sickle cell anaemia [22]. *Jatropha tanjorensis* has received a lot of attention due to its potential health benefit, availability and affordability [23, 24]. Its primary use is for fencing, and as medicine [25]. Phytochemical screening of *Jatropha tanjorensis* leaf revealed that it contains bioactive principles such as alkaloids, flavonoids, tannins, cardiac glycoside, anthraquinones and saponins [23]. The pharmacological studies revealed that the plant showed some wide range of biological activities, which include antihypertensive, antioxidant, antimicrobial, antimalarial, hypoglycaemic, hypolipidaemic and haematological activities [25].

Anacardium occidentale L. (cashew) belongs to the family 'Anacardiaceae', which is native to Brazil [26]. This family consists of 400-600 species. In Nigeria, It is commonly called 'Kashew' (Hausa), 'Kaju' (Yoruba), 'Kausu' (Igbo), 'Shase' (Tiv) and 'Kashiwu' (Nupe) [27, 28, 29]. *Anacadium occidentale* has been cultured essentially, and whole fruit is used for medicinal and food purposes, e.g., apple and kernel. *Anacadium occidentale* gained its importance during World War II due to the utilization of its significant by-product, the *Anacadium occidentale* nut shell liquid [30]. *Anacadium occidentale* kernels have shown low-density lipoprotein cholesterol levels and coronary risk diseases [31]. *Anacadium occidentale* part contains proteins and fats. The proteins include lysine, cysteine, arginine tyrosine, valine, and many vitamins like vitamin C, E, and D [32]. The key component of *Anacadium occidentale* is anacardic acid. It is used as an antimicrobial, killing bacteria, fungi, worms and protozoa [33]. *Anacadium occidentale* gum has been used widely for many health-related issues. These are less in saturated fatty acids and more in unsaturated fatty acids. Its health benefits have been used to decrease the risk of cardiovascular diseases, oxidative stress, inflammation, high cholesterol, and diabetes [30]. *Anacadium occidentale* nuts are used for the treatment of obesity, diabetes, heart disease, urinary disorders, digestive disorders, and many other clinical applications like bone relaxation, cold and flow, etc. It also has importance in cancer and protects from aging [34]. The young and tender leaves of *A. occidentale* are a popular herb consumed raw as ulam and sometimes blanched to reduce their stringent taste. In traditional medicine, leaves are used for treating dysentery [35], malaria [36], vaginal douche [37], diarrhoea and piles, and an infusion of bark and leaves are applied to relief toothache and sore gums [38]. Other uses of leaves include remedy for rheumatism and hypertension [39, 40]. However, there have been several research on the uses of *Anacadium occidentale* and *Jatropha tanjorensis* in the treatment or management of certain diseases, but there is little or no research on the determination

of the LD_{50} of ethanol- methanol (1:1) extracts of these plants as well as their effects on serum lipid profile of Wistar rats, hence, the need to conduct this research.

2. Material and methods

2.1. Chemicals/Reagents

Commercially available kit for chemical analyses like serum cholesterol, HDL-c, LDL-c and triglyceride were purchased from Biosystems S.A. (Barcelona, Spain). All other chemicals of analytical grade were obtained from Merck (Darmstadt, Germany).

2.2. Plant Materials

Freshly collected leaves of *Anacadium occidentale* and *Jatropha tanjorensis* were obtained from local garden at Bebi, Obanliku Local Government Area of Cross River State, Nigeria. The plants specimen were identified and authenticated in the Department of Plant Science, Cross River University of Technology (CRUTECH), Calabar, Cross River State, and the voucher numbers; CRUTECH/PSB/0045 for *Anacadium occidentale* and CRUTECH/PSB/0046 for *Jatropha tanjorensis* were deposited in the herbarium. The leaves were thoroughly washed, then air-dried at room temperature.

2.3. Extraction of Plant Samples

The leaves were sorted to eliminate any dead matter and other unwanted particles. The leaves were air-dried for 21 days and then grinded in a domestic mixer grinder and coarse powder was prepared. 100g of each of the plant samples was extracted with methanol (500mls) and ethanol (500mls) in a Soxhlet extractor for 72 hours at 60^{o}C respectively. The extract was evaporated to dryness at 40^{0}C. The obtained extracts was in chocolate colour with aromatic odour [41].

2.4. Experimental Animals

Twenty five (25) male Wistar rats weighing between 180 to 220g were used for the lipid profile study while eighteen (18) Wistar rats were used for the acute toxicity study. The animals were maintained under laboratory conditions of humidity, temperature (23 to 25°C) and 12 hours light-dark cycle in the Animal House of Department of Medical Biochemistry, Cross River University of Technology, Okuku Campus and allowed free access to standard grower's mash (Hybrid Feeds Ltd., Kaduna) and water *ad libitum*. The animals were acclimatized for two weeks.

2.5. Determination of Lethal Dose (LD_{50}) (Acute Toxicity Study)

The determination of median lethal dose (LD_{50}) of the ethanol and methanol extract was carried out by procedure described by [42]. Eighteen (18) albino Wistar rats weighing 180 to 220 g were used. The test involved two stages. In phase I, the rats were grouped into three (3) groups of three (3) rats each. They were administered orally 10, 100 and 1000 mg/kg^{-1} b.wt., of the extracts respectively. In the phase II, the animals were divided into three (3) groups of three (3) rats each also and administered the graded doses of 1600, 2900 and 5000 mg/kg^{-1} b.wt of extracts and then observed for 24 hours for behaviour as well as mortality. It was calculated to be given 10% of the extracts to low doses and 20% of the extracts to high doses.

Then, the LD_{50} was derived based on the formula:

$$LD_{50} = \sqrt{D_0 \times D_{100}}$$

Where, D_0 = Highest dose that produced mortality
D_{100} = Lowest dose that produced mortality

2.6. Experimental Design

Twenty five (25) male Wistar rats weighing 180 to 220g were used for the study while Eighteen (18) Wistar rats were used for the acute toxicity (LD_{50}) study. After acclimatization, the animals were divide randomly into six (6) groups of three (3) rats each for phase I and II acute toxicity study. Animals for lipid profile study were divided into five (5) groups, each group containing five animals (n = 5). Group I: Normal Control; treated with normal saline; Group II: Experimental rats administered low dose (400 mg/kg^{-1} b.wt.) of *Anacadium occidentale* extract; Group III: Experimental rats administered high dose (800 mg/kg^{-1} b.wt.) of *Anacadium occidentale* extract; Group IV: Experimental rats administered low dose (400 mg/kg^{-1} b.wt.) of *Jatropha tanjorensis* extract; and Group V: Experimental rats administered high dose (800 mg/kg^{-1} b.wt.) of *Jatropha tanjorensis* extract.

2.7. Animal Sacrifice and Serum Collection

At the end of the administration, the Wistar rats were weighted using weighing balance, euthanized under chloroform. The abdominal region was opened long the linear Alba, dissected using surgical blade to expose the organs. Blood sample was collected through cardiac puncture using a sterile needle. A syringe was used to collect the blood and transferred into a properly labeled plain sample bottles. It was centrifuged at 3000rpm for 10 minutes. A sterile Pasteur pipette was used to transfer the serum from the clotted blood into a serum container.

2.8. Lipid Profile Assays

2.8.1. Determination of Total Cholesterol (TC)

Cholesterol (TC) was estimated based on the method of [43].

2.8.2. Determination of Triglycerides (TG)

Triglycerides (TG) was determined according to method of [44].

2.8.3. Determination of High Density Lipoprotein Cholesterol (HDL-c)

High density lipoprotein cholesterol (HDL-c) concentration was estimated according to the method of [45], using Randox kit.

2.8.4. Determination of Low Density Lipoprotein Cholesterol (LDL-c) and Very Low Density Lipoprotein Cholesterol (VLDL-c)

Very low density lipoproteins cholesterol (VLDL-c) and low density lipoprotein cholesterol (LDL-c) were estimated or derived from TC, TG and HDL-c according to Friedewald's formula for lipids derivation [46].

2.9. Statistical Analysis

Data were recorded as mean and standard error of the Mean. Statistical difference between the means was determined by one-way ANOVA using SPSS 16.0. Any significant difference between means was assessed by and $P<0.05$ was accepted as the significant level.

3. Results

The results in table 1 revealed the effect of administration of ethanol-methanol (1:1) extracts of *Anacadium occidentale* and *Jatropha tanjorensis* on serum lipid profile of Wistar rats. Following the administration of the extracts, the extracts produce a significant (*P<0.05*) decrease in total cholesterol (TC) of all the groups except group IV compared with the normal control (NC). Group III and IV administered high dose of *Anacadium occidentale* and low dose of *Jatropha tanjorensis* respectively produced a significant (*P>0.05*) decrease in TC compared with each other.

The extract produced a significant (*P<0.05*) increase in total triglycerides (TG) in all the groups compared with control. However, there was a significant (*P<0.05*) decrease in TG of the groups administered *Jatropha tanjorensis* (IV and V) compared with those administered *Anacadium occidentale* (II and III). High density lipoprotein cholesterol (HDL-c) level was significantly (*P<0.05*) increased in group III only compared with control. Low density lipoprotein cholesterol (LDL-c) level was significantly decreased in groups that were administered with high dose of *Anacadium occidentale* and *Jatropha tanjorensis* respectively compared with control.

Also, the extract produced a significant (*P<0.05*) increase in very low density lipoprotein cholesterol (VLDL-c) in all the groups compared with control. However, there was a significant (*P<0.05*) decrease in VLDL-c of the groups administered *Jatropha tanjorensis* (IV and V) compared with those administered *Anacadium occidentale* (II and III). The LDL-c/HDL-c ratio showed no significant (*P>0.05*) difference between groups II, V and the control, however group III was significantly decreased compared with the rest of the groups, conversely, that of group IV was significantly increased compared with the rest of the groups.

The acute toxicity (LD_{50}) of the ethanol-methanol extract of *Anacadium occidentale* and *Jatropha tanjorensis* leaves showed no death or adverse reaction in the Wistar rats administered with various doses of the extract. However, the Wistar rats administered 5000 mg/kg^{-1} of *Jatropha tanjorensis* showed death or adverse reaction (Table 2).

Table 1 Result showing lipid profile of Wistar rats administered with Ethanol - Methanol (1:1) Extracts of *Anacadium occidentale* and *Jatropha tanjorensis*

GROUPS	TC (mg/dL)	TG (mg/dL)	HDL-c (mg/dL)	LDL-c (mg/dL)	VLDL-c (mg/dL)	LDL-c /HDL-c
NC	190.36±0.80[a]	123.69±1.34[a]	46.4±1.00[a]	168.88±1.48[a]	24.92±0.27[a]	3.65±0.10[a]
LAO	178.40±1.43[b]	224.00±2.28[b]	46.6±1.32[a]	177.20±2.19[b]	45.20±0.28[b]	3.84±0.14[a]
HAO	157.60±2.59[c]	217.00±1.39[c]	53.0±1.39[b]	152.20±1.93[c]	43.40±0.28[b]	2.88±0.04[b]
LJT	187.70±2.00[a]	150.00±3.19[d]	41.2±0.33[c]	177.72±1.60[b]	30.76±1.43[c]	4.32±0.05[c]
HJT	160.88±2.11[c]	182.20±0.72[e]	41.4±0.22[c]	155.92±2.04[c]	36.44±0.14[d]	3.77±0.05[a]

Values are expressed as Mean ± SD. Identical superscript (i.e. a) means there is no significant difference between the comparing group P>0.05. Non – identical superscripts (i.e. a, b, c, d, e) means there is significance between the comparing groups at P<0.05. Legend**:** NC: Normal control; LAO: Low dose of *Anacadium occidentale*; HAO: High dose of *Anacadium occidentale*; LJT: Low dose of *Jatropha tanjorensis* and HJT: High dose of *Jatropha tanjorensis*.

Table 2: Phase I and II of the median lethal dose of *Anacadium occidentale* and *Jatropha tanjorensis*

Groups	Dosage (mg/kg^{-1} b.wt)	Mortality	
		***Anacadium occidentale* extracts**	***Jatropha tanjorensis* extracts**
Phase I			
Group 1	10	0/3	0/3
Group 2	100	0/3	0/3
Group 3	1000	0/3	0/3
Phase II			
Group 1	1600	0/3	0/3
Group 2	2900	0/3	0/3
Group 3	5000	0/3	3/3

Values are Mean ± standard derivation (n = 3)

4. Discussion

Lipids are group of naturally occurring molecules that include fats, waxes, sterols, fat-soluble vitamins, monoglycerides, diglycerides, triglycerides, phospholipids and others. The main biological functions of lipids include storing energy, signaling and acting as structural component of cell membranes [47]. Lipids may be broadly defined as hydrophobic or amphiphilic small molecules [48]. Although humans and other mammals use various biosynthetic pathways to both break down and synthesize lipids, some essential lipids cannot be made this way and must be obtained from the diet [48]. In order to ensure that the body lipid concentration is normal, lipid profile test is done.

In recent years, many people have been unaware of the benefits of knowing one's profile. Lipid profile is a panel of blood tests that serves as an initial screening tool for abnormalities in lipids, such as cholesterol and triglycerides. There are two common concerns people have about lipids in their diet. One is their high caloric level which may result in undesirable weight gain. The other is their association with high cholesterol level which is a risk factor for cardiovascular diseases [49]. The effect of ethanol-methanol extracts of *Anacadium occidentale* and *Jatropha tanjorensis* on total cholesterol, triglycerides, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and very low-density lipoprotein cholesterol of Wistar rats were investigated. The non-toxicity of the ethanol-methanol extracts of *Anacadium occidentale* leaves was observed up to 5000 mg/kg^{-1} b.wt (highest dose), suggesting the safety of the extracts for human and animal consumption and complements. However, non-toxicity was observed in ethanol-methanol extracts of *Jatropha tanjorensis* leaves up to 2900 mg/kg^{-1}b.wt. But Wistar rats administered 5000 mg/kg^{-1} b.wt of *Jatropha tanjorensis* died, indicating that *Jatropha tanjorensis* is highly toxic than *Anacadium occidentale*.

Cholesterol is the principal sterol synthesized by all animals and occurs mainly in the cell membrane due to its amphipathic nature [50]. Its synthesizes begins with the mevalonate or HMG-CoA reductase pathway, the target of statin drugs, which encompasses the first 18 steps, then followed by 19 additional steps to convert the resulting lanosterol into cholesterol via either of two pathways, the Bloch Pathway, or the Kandutsch-Russell Pathway [51, 52]. It is reportedly a major cause of cardiovascular derangements such as atherosclerosis, myocardial infarction and coronary heart diseases [1]. In this study, the plant extracts produced a decreased in serum cholesterol which might be due to a reduce absorption from the intestine by binding with bile acid within the intestine and increasing bile acid secretion [53], or due to the presence of saponins, a phytochemical which forms insoluble complexes with cholesterol or their bile salt precursor, thus making them unavailable for absorption [54]. Therefore, it implies that the plant extracts possess anticholesterolaemic activities.

Triglyceride is an ester derived from glycerol and three fatty acids and the most common type of lipid in the body. Triglycerides are the main constituents of body fat in humans and other vertebrates, as well as vegetable fat [50]. They are also present in the blood to enable the bidirectional transference of adipose fat and blood glucose from the liver, and are a major component of human skin oils [55]. It is not cholesterol but it is measured because when it is high and high density lipoprotein cholesterol (HDL-c) is low, it may results in atherosclerosis and coronary heart diseases [1, 56]. Hypertriglyceridemia is a high level of triglyceride in the blood and could results in cardiovascular disease [57]. In this study, it was observed in all the test groups that the plant extracts elevates triglyceride levels.

Low density lipoprotein cholesterol (LDL-c) transports cholesterol form the liver to the exact site where it is going to be utilized. If there is excess of LDL-cholesterol, it may initiate the process of atherosclerosis [54]. It transports about 60-70 % of total cholesterol. Therefore, an increase in TC level consequently increase LDL-c [58]. The plant extracts administered at high doses appeared to have a decreased in serum LDL-c level, hence a non-predisposition to atherosclerosis and other cardiovascular related diseases. Atherosclerosis narrows the area where blood flows through the vessels. This reduces the supplied with the blood, and it is perfect place for clot formation. If there is too much of LDL-cholesterol, it can lead to many other illness such as angina, coronary heart diseases, heart attacks, stroke and hypercholesterolemia [1, 59].

High density lipoprotein cholesterol (HDL-c) is an anti-atherogenic lipoprotein which transports cholesterol from peripheral tissues back to the liver where it is broken down to bile acids [60, 61, 62], as revealed in the group that was administered with high dose of *Anacadium occidentale* only. The inhibition of HMG-CoA reductase (a microsomal enzyme which catalyze the rate of limiting step in cholesterol synthesis pathway), reduces LDL-c and concurrently increase HDL-c [63]. Increased level of HDL-cholesterol observed is associated with healthy heart thereby reduce risk for cardiovascular diseases development and related complications such as stroke, myocardial infarction and death [64, 65]. Also, this could possibly be due to increasing activity of lecithin-cholesterol acyl transferase (LCAT), an enzyme responsible for incorporating free cholesterol into HDL-c [66], thereby promoting reverse cholesterol transport and competitively inhibiting the uptake of LDL-c by endothelial cells and preventing the generation of oxidized LDL-c [67]. Previous studies revealed that one out of three deaths would be due to cardiovascular disease and the prevailing factors remain elevated levels of serum total cholesterol (TC), low density lipoprotein cholesterol (LDL-c), triglyceride (TG) and decreased level of high density lipoprotein cholesterol (HDL-c) [68, 69]. These Prevailing factors predisposing to cardiovascular disease was not observed in the study. The effect was dose dependent with respect to *Anacadium occidentale*.

Moreover, the LDL-c/HDL-c ratio is often used as an index for cardiovascular disorders [70, 71, 72], and in this study the LDL-c/HDL-c ratio in groups that were administered low dose of *Anacadium occidentale* and high dose of *Jatropha tanjorensis* showed non-significant difference compared to the control. However, the group that was administered high dose of *Anacadium occidentale* revealed a decreased compared to the control, the reverse was the case in the group administered with low dose of *Jatropha tanjorensis.* This suggests the anti-atherogenic potential of the *Anacadium occidentale* and *Jatropha tanjorensis* extract, however the effect is dose-dependent and revealed more effective when high dose of *Anacadium occidentale* is administered.

5. Conclusion

The study suggests that the plant extracts exhibit lipid lowering effects which could be employed in the treatment of metabolic disorders such as atherosclerosis and cardiovascular diseases by the inhibition of biosynthesis, absorption and secretion of lipids, which may be possibly due to the presence of secondary metabolites in the plants used. However, further research is needed to investigate the anti-hyperlipidaemic components in *Anacadium occidentale* and *Jatropha tanjorensis* and their mechanism of actions.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there are no conflict of interests.

Statement of ethical approval

The research study was carried out according to the guidelines approved by CRUTECH Institutional Research Ethical Committee (IREC) following the principle laid down in the Declaration of Helsinki (1964), as revised in 2013 and National Institute of Health (NIH) Principles of Laboratory Animal Care. No human participants were involved in the study.

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