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Facile One-Pot Strategy for Radiocoplexation of [99mtc]-Nitrido-Nebracetam for Brain Imaging: Biological Evaluation, Optimized Chromatographic Separation and Labeling Conditions

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In Loving Memory of Late Professor Doctor ""Mohamed Refaat Hussein Mahran""

Abstract

Glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs) are central to regulating excitatory synaptic transmission in the central nervous system (CNS) Therefore, the aim of this research is to study the biodistribution to demonstrate the concentration of [99 mTc]-nitrido-nebracetam in the target organ (brain) using healthy groups of Swiss albino mice. The radiotracer [99mTc]-nitrido-nebracetam ([99mTc]-N-Neb) complex was labelled using the core [99mTc≡N] 2+.Many factors have been studied to optimize high radiochemical yields (>97.5).Quality control studies were made perfectly. A process of biodistribution indicated that this complex, [99mTc]-N-tamsulosin, was washed out through the urinary pathway within 3 hours after injection. In addition, the brain uptake of this complex was 11.88% after 30 min post-injection as a novel probe for (AMPA) receptor targeting. Hence, the radiotracer of [99mTc]-N-Neb could be used as a radiotracer of brain imaging through AMPA receptor.

Keywords: [^{99m}Tc]-nitrido-nebracetam, [^{99m}Tc]-nitrido core, biological evaluation, brain, imaging

Introduction

A lot of methods were used in brain imaging, either direct or indirect. Nuclear medicine has rapidly progressed in the last 25 years, mainly due to the successful imaging of brain tumors with radiopharmaceuticals targeting changes in the blood-brain barrier. Magnetic resonance imaging (MRI) and positron emission tomography (PET) are brain imaging techniques that allow researchers to visualize and study the structure of the brain. For effective brain imaging, it is essential to choose compounds that can penetrate the brain, provide functional data, including regional perfusion and metabolism, and possess a strong binding affinity to selectively get attached to the receptors, such as AMPA inhibitors [1].In the central nervous system (CNS), glutamatergic α-amino-3- Hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs) play a crucial role in controlling excitatory synaptic transmission. Their swift kinetics set them apart from N-methyl-aspartate receptors (NMDARs), enabling the postsynaptic membrane to depolarize quickly and enabling the high-fidelity transmission of electrical impulses between neuronal cells. The postsynaptic membrane of excitatory synapses is home to α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors, which are very dynamic and can enter and exit synapses both constitutively and activity-dependently. The postsynaptic content of AMPARs is modulated by changes in their quantity, subunit makeup, post-translational modifications, and interactions with scaffolding and auxiliary proteins. This enables quick and precise control over synaptic strength [2].

Racetams are considered one of the compounds that have a pyrrolidone ring. Like drugs of nebracetam (Figure 1A), piracetam, pramiracetam, phenylpiracetam, aniracetam, and oxiracetam are nootropics [2]. However, anticonvulsant drugs like levetiracetam, brivaracetam, and seletracetam are anticonvulsants. As with some ampakines, many racetams, like nebracetam, oxiracetam, pramiracetam, piracetam and aniracetam, levetiracetam, brivaracetam, and seletracetam, are positive allosteric modulators of the AMPA receptor [3].Since the process of radiological imaging of the brain is a complex one that depends on the ability of the drug to cross the blood-brain barrier as well as the ability of the tracer to localize on the brain,. We had to conduct many, many experiments related to brain

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imaging to reach the optimal condition for that imaging.

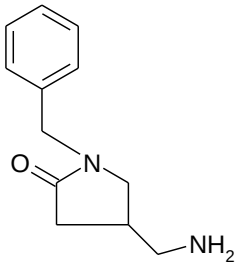

Figure 1A. Chemical structure of nebracetam

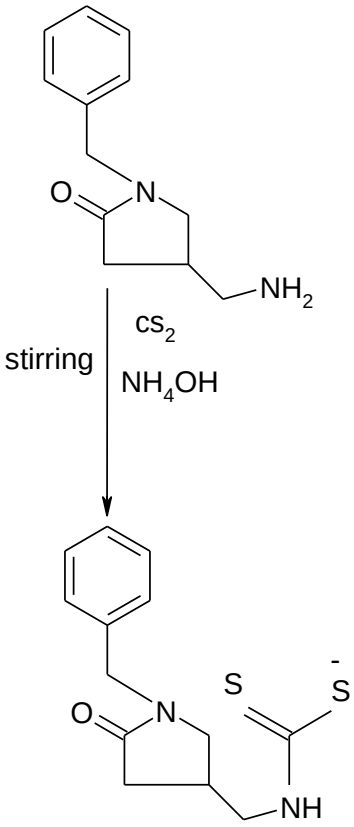

Fig. 1B Schematic representation of synthesis of dithiocarbamate of nebracetam

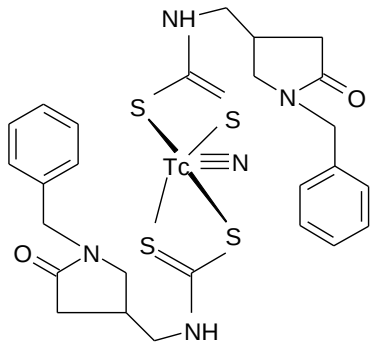

Fig. 1C Structure of [99mTc]-nitrido-nebracetam complex

Despite the conduct of many, many experiments in this scope [4–14], there are still two fundamental points around which this research revolves, in the past or present, which are the percent of the complex located in the brain and the time it remains in the brain. In this work, a new radiotracer, [99mTc]-N-Neb, was systematically developed (Figure 1C). It is preferable to use [99mTc]-N-nebin instead of many radiotracers studied previously, like [15–17], since its concentration in the target organ (brain) is high compared to this radiotracer. Using healthy groups of normal mice of Swiss albino mice, a biodistribution study was carried out to demonstrate the concentration of this radiotracer in the target organ (brain).

Materials and Methods

Experimental

Reagents

Nebracetam was purchased from Med Chem Express, USA, propylenediaminetetraacetic acid (PDTA), aqueous ammonia solution and carbon disulfide purchased from Sigma-Aldrich Chemical Company, St. Louis, MO, USA. Thin layer chromatography (TLC) aluminum sheets (20 × 25 cm) SG-60 F_{254} were supplied by Merck. Whatman paper number (PC) 1, Whatman International Ltd, Maidstone, Kent, UK. All chemicals were of analytical or clinical grade and were used directly without further purification unless otherwise stated. Double distilled water was used for all experiments for the preparation of solutions, dilution and washing purposes.

Apparatus

Mass Spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70eV. Elemental analyses were carried out on ELEMENTAR VIRO EL, Germany instrument at the Micro analytical Center, National Research Centre (Cairo, Egypt). All reactions were followed by TLC (silica gel, aluminum sheets 60 GF_{254}, Merck), and were detected at 266 nm. A well-type NaI scintillation γ-Counter model Scalar Ratemeter SR7 (Nuclear Enterprises Ltd., USA) was used for radioactive measurement. Paper electrophoresis (PE) apparatus: E.C. Corporation (Albany, OR, USA).

Preparation of dithiocarbamate Nebracetam, $[^{99m}Tc{\equiv}N]^{2+}$core and $[^{99m}Tc]$-N- Nebracetam

Preparation of dithiocarbamate tamsulosin(see figure 1B) has been carried out by the addition of a solution of carbon disulfide (0.5 mL) in ethanol (1: 4 v/v). Followed by a pre-cooled solution of nebracetam(5 mg, 57 µmol) add to aqueous ammonia (2 mL) at 0°C under constant stirring. After that the resultant reaction mixture is magnetically stirred overnight at 37 ^{0}C. After completion of the reaction, the crude dithiocarbamate was obtained by evaporating the solution under vacuum. The

dithiocarbamate Nebracetamwas re-crystallized from ethanol/diethyl ether. The pure product, thus obtained, was characterized by mass spectrometry and elemental analysis with a yield of 57% and melting point (87-89°C). This core, $[^{99m}Tc{\equiv}N]^{2+}$was synthesized by adding exactly 50 µL of stannous chloride dihydrate (0.05 mg) in aqueous hydrochloric acid (0.1N), 5 mg of succinicdihydrazide and 5 mg of 1,2-Diaminopropane-N,N,N′,N′-tetraacetic acid , sodium dihydrogen phosphate (0.5 mg) and disodium hydrogen phosphate (5.8 mg) are added. Then, the mixture produced was preserved at 37 ^{0}C after the addition of one mL of pertechnetate ion, $Na^{99m}TcO_4^-$ (~37 MBq, 1 mCi), for30min reaction time. The ^{99m}Tc-nitrido intermediate thus prepared was characterized by TLC and HPLC. The [^{99m}Tc]-N-Nebracetam core radiotracer has been prepared by adding 0.5 mL solution of the freshly prepared nitride core with 3 mg of the dithiocarbamate silodosin dissolve in ethanol (0.5 mL). The resulting solution was thoroughly vortexed and subsequently incubated at 37 ^{0}C at pH 6 (phosphate buffer) and 30min reaction time. High performance liquid chromatography (HPLC) analysis gave a purity for [^{99m}Tc]-N-Nebracetamof >98% as shown in Fig (2A-B) [15-17].

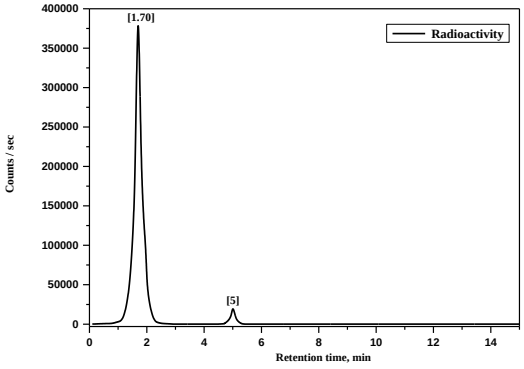

Fig.2A HPLC of $[^{99m}Tc{\equiv}N]^{2+}$core >99%, t_R =1.70 min,

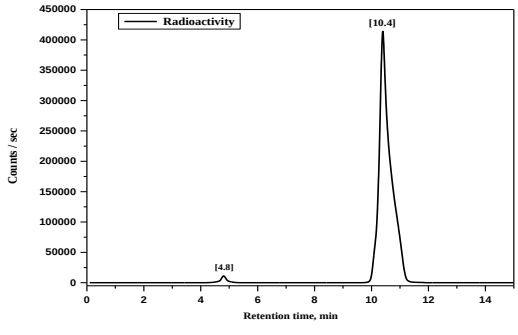

Fig.2B HPLC of [^{99m}Tc]-nitrido-Neb complex>98%. The R_t values of free $[^{99m}Tc{\equiv}N]^{2+}$core and [^{99m}Tc]-nitrido-Neb complex were 4.8 and 10.4 min, respectively.(mean yield % ± SD, n = 3).

Radiolabeling procedure

A drug amount, the pH of the reaction mixture, and reaction time of the mixture were examined at room. A volume of two mL of nitride core, $[^{99m}Tc{\equiv}N]^{2+}$ reaction mixture, 200µgNebracetam, at pH 6 (phosphate buffer,100 µL). This mixture was stirred with a magnetic stirrer at temperature of 37 ^{0}C for 30 min giving high percent radiochemical yield. The effect of enormous reaction factors like the substrate amount (50-1000µg), the pH of the reaction mixture (2–12), the time of reaction (1–60 min) was tested giving high efficiency of radiochemical yield. The radiotracer [^{99m}Tc]-N-Neb has been purified by high performance liquid chromatography, HPLC. Fractions of a volume 1.0 mL were collected separately up to a volume of 15 mL and counted with a γ-ray scintillation counter [15-17].

Radiochemical analysis of [^{99m}Tc]-N-Neb

he radiochemical conversion % of [^{99m}Tc]-N-Nebwas determined using aluminum-backed silica gel GF_{254} plates. A volume of two µL (1.60 MBq) reaction mixture was placed above the lower edge, which was allowed to evaporate.The plate was developed in two different solvent systems of normal saline 0.9 % and ethanol: chloroform: toluene: 0.5 M ammonium acetate (6:3:3:0.5 v/v/v/v). The strips were removed, dried and cut into one cm segments and assayed for radioactivity using SR.7 gamma counter.Additionally, the colloidal impurities were separated by the filtration of the reaction mixture through a 0.22 µm Millipore filter at a suitable pressure [15-17].The radiochemical conversion was further confirmed by paper electrophoresis (PE) using Whatman paper no1 (2 cm width and 47cm length), 2µl of the reaction mixture was placed at 12 cm from the negative electrode edge of the paper sheet. Electrophoresis was carried out for 3 hour at a voltage of 300V using normal saline (0.9% w/v NaCl solution) as electrolytes. On completion of development, the paper was removed, dried, cut into1 cm. wide strips, and the strip counted in a γ-counter. The percentage radiochemical conversion was calculated as the ratio of the radioactivity of [^{99m}Tc]-N-Neb to the total activity multiplied by 100 [15-17]. High performance liquid chromatography analysis (HPLC) was used for purification of [^{99m}Tc]-N-Neb by direct injection of 15µL of the reaction mixture. An isocratic elution system was performed on the column reversed-phases C_{18} (250x4 mm, 5µm, Lischrosorb), build in HPLC Shimadzu model consisting of pumps LC-9A with a Rheodyne injector, with a mobile phase of H_2O& methanol (50:50 v/v) and UV spectrophotometer detector (SPD-6A) was 266 nm wavelengths. The mobile phase was delivered at flow of 1.0 mL/min. Also $[^{99m}Tc{\equiv}N]^{2+}$core can be detected by injecting the reaction into reversed-phases C_{18} (Lichrosorb, 150 mm x 4.6 mm, 5µm) column gradient elution system

in which the mobile phase consisted of (solvent A) water and (solvent B) acetonitrile. The gradient system HPLC system started with 100% A/0% B with a linear gradient to 0% A/100% B from 0 to 30 min with flow rate was 1.0 mL/min [15-17].

The in-vitro stability of [^{99m}Tc]-N-Neb was studied in two different media.

Stability of [^{99m}Tc]-N-Neb in saline

The radiotracer,[^{99m}Tc]-N-Neb complex [5 µL (2.55 MBq)] radiotracer was checked at 37^{o}C for the stability test in saline at optimum condition then, the experiment was carried out by allowing the radiotracer to stand for 24 hour at ambient temp by TLC or HPLC [15-17].

Stability of [^{99m}Tc]-N-Neb in serum

A volume of 1.9 mL of normal human serum was mixed with 0.1 mL [0.17 MBq] of [^{99m}Tc]-N-Neb complex together and incubated at 37oC for 24 hours. About 0.2 mL was withdrawn and analyzed by HPLC [15-17].

Biodistribution and animal studies

Animal experiments were approved by the Ethics Committee of the Department of Labeled Compounds. Male Swiss albino mice (40 to 50 g) were used in this experiment. Six groups of normal group (5 animals were used for a total of 30 mice, 6 weeks old) was intravenously injected with 0.2 mL (3.6 MBq) of [^{99m}Tc]-N-Nebcomplexadjusted to physiological pH via the tail vein. To measure the organ distribution (by time point) [^{99m}Tc]-N-Neb complex, animals were sacrificed at 5 min, 15 min, 30 min, 60 min, 2 hrs, and 3 hrs [15-17,18-30].Corrections for background radiation and physical decay were made during the experiments. P value results are reported using the 2-tailed test. The significance level was set at $P < 0.05$.

Results and Discussion

Evaluation of radiochemical yield by TLC, PE and HPLC:

The radiochemical conversion was calculated on TLC and PE by the percent ratio of [^{99m}Tc≡N]$^{2+}$core intermediate at R_f (0.0−0.1) or R_f (0.8-1) to free $^{99m}TcO_4^-$ at R_f (0.4−0.6) according to solvent used. Colloids substances such as $Tc(OH)_2$, $Sn(OH)_2$, $Tc(OH)_4$ or ^{99m}Tc-tin colloid were also eliminated by 0.22 µm Millipore filter at a suitable pressure. From the paper electrophoresis results, [^{99m}Tc]-N-Neb complexremained at 0 cm from the spotting point (neutral labeled compound). While the free$^{99m}TcO_4^-$ moved towards the anode and nitride core intermediate moved towards the cathode. An optimum conversion of>98% was achieved [31-40]. High performance liquid chromatography (HPLC) analysis gave a purity for [^{99m}Tc≡N]$^{2+}$core intermediate of 98%, R_t values of the core and $^{99m}TcO_4^-$ were 1.70 and 5.0 min (Fig.2A). The R_t values of [^{99m}Tc]-N-Neb complexand [^{99m}Tc≡N]$^{2+}$core intermediatewere 10.4 and 4.8 min, respectively (Fig. 2B).

Characterization of dithiocarbamate Nebracetam

The chemical structure of dithiocarbamate Nebracetam (molecular formula,[$C_{13}H_{15}N_2OS$],) was confirmed by the following: Mass spectrometry shows a molecular ion peak at m/z 247.59 [M–S] that was observed as in many literatures [15-17]. Elemental analysis calculated was C 55.91; H 5.38 and N 10.04%. The obtained results showed: C 55.93; H 5.37 and N 10.11%.

Optimization of reaction

Figure 3 shows the influence of varying amounts of substrate (Nebracetam,Neb) on radiochemical yield [40-55]. The optimal radiochemical conversion to [^{99m}Tc]-N-Nebcomplex was 97.5% with 200 µg of substrate and free [^{99m}Tc≡N]$^{2+}$ core at 7.6 MBq [56-70].The effect of reaction time was also studied, and, as shown in Figure 6, the maximum conversion to [^{99m}Tc]-N-Nebcomplex occurred at 30 min.(Figure4) [70-80].In addition, pH is an important factor in labeling process (Figure 6) which needs to be controlled, pH 6 proving optimal which may reflect in part the stability of [^{99m}Tc]-N-Nebcomplex (98.5 %) [80-90].The optimum radiochemical conversion is significantly changed by changing pH from highly acidic to highly basic [81-100]. The in vitro stability of the radiotracer [^{99m}Tc]-N-Nebcomplex was evaluated in two different media. The radiotracer,[^{99m}Tc]-N-Nebcomplex was found to be stable in saline for up to 24 hours. Contrary to this, the purity of [^{99m}Tc]-N-Nebcomplex in serum decreased to 90.0% after 12 hours, and at 24 hours, it decreased to 85% (Tables 1,2).

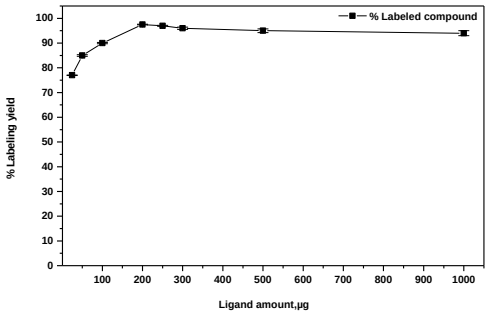

Fig.3 Effect of Neb amount on the radiochemical yield % of [^{99m}Tc]-nitrido-Neb complex. Conditions: 25-1000µg of Neb, 50µg Sn (II), pH 6 and 30 min. reaction time, (mean yield % ± SD, n = 3).

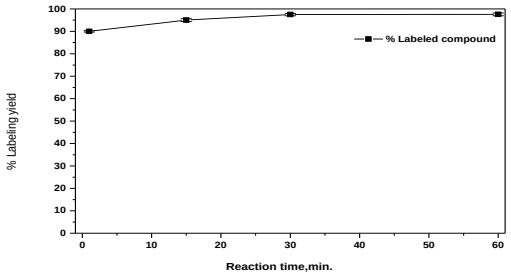

Fig. 4Effect of reaction time on the radiochemical yield % of [^{99m}Tc]-nitrido-Neb complex. Conditions: 200µg ofNeb, 50 µg Sn (II), pH 6 and (1-60) min. reaction time, (mean yield % ± SD, n = 3).

Table (1): In-vitro stability in saline of [^{99m}Tc]-N-Nebcomplex

Time (h)	[^{99m}Tc]-N-Nebcomplex	[^{99m}Tc≡N]$^{2+}$core
3	97.5 % ± 0.79	2.5 ± 0.66
6	97.4 ± 0.88	2.6 ± 0.98
12	97.4 ± 0.91	2.6 ± 0.87
24	97.0 ± 0.55	3.0 ± 0.31

Values represent the mean ± SEM, n = 3

Table (2): In-vitro stability in serum of [^{99m}Tc]-N-Nebcomplex

Time (h)	[[^{99m}Tc]-N-Nebcomplex	[^{99m}Tc≡N]$^{2+}$core
3	97.5 ± 0.37	2.5 ± 0.15
6	97.0 ± 0.70	3.0 ± 0.19
12	90.0 ± 0.66	10.0 ± 0.59
24	85.0 ± 0.39	15.5 ± 0.70

Values represent the mean ± SEM, n = 3

Biodistribution study

Table 3 shows a biodistribution in normal mice of the [99mTc]-N-Neb complex in various body fluids and organs. Radioactivity levels are reported as the average percent injected dose per organ tissue (%ID/organ ± SD).The kidney uptake was found to be 3.44% at 5 minutes after injection and decreased to 10.29% at 3 hours p.i.. Also, the [99mTc]-N-Neb complex accumulates through urine to give 44.11 at 3 hours p.i.Thus, the [99mTc]-N-Nebcomplex, a highly radiotracer, accumulates with selective localization in the target organ, the brain, through theAMPA receptor more than [99mTc]-N-histamine (4.5% ID/organ at 30 min), [99mTc]-N-piracetam (7.15 % ID/organ at 30 min), and [99mTc]-N-oxiracetam (10.6 % ID/organ at 30 min) complexes [15–17]. Most organ uptake was cleared rapidly during the 60 minutes post-injection [101–122].

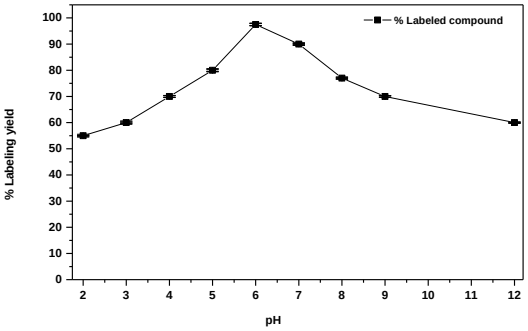

Fig. 5 Effect of pH on the radiochemical yield of [^{99m}Tc]-nitrido-Neb complexConditions: 200 µg of Neb, 50 µg Sn (II), pH (4-12) and 30 min. reaction time, (mean yield % ± SD, n = 3).

Conclusion

An optimized protocol for the synthesis of the [^{99m}Tc]-N-Neb complexwith excellent radiochemical conversion (>97.5%) has been developed. Biodistribution studies indicated that the radiotracer [^{99m}Tc]-N-Nebcomplex has a high prostate uptake of 11.88 % ID/organ at 30 min post injection. The[^{99m}Tc]-N-Neb complex, is superior to previously reported radiotracer such as [^{99m}Tc]-N-histamine(4.5, % ID/organ at 30 min),[^{99m}Tc]-N-piracetam(7.15 % ID/organ at 30 min), [^{99m}Tc]-N-oxiracetam(10.6,% ID/organ at 30 min)complexes.

Table 3. Biodistribution of [^{99m}Tc]-N-Neb in normal mice at different times

Organs & body fluids	% I.D./organ at different times post injection (Mean ± SEM, n = 5)					
	5 min	15 min	30 min	60 min	120 min	180 min
Urine	6.11 ± 0.08	11.5 ± 0.44	19.8 ± 0.54	29.8 ± 0.29	37.33 ± 0.99	44.11 ± 1.11
Kidneys	3.44± 0.06	5.19 ±0.03	9.18 ±0.02	18.15± 0.01	22.17 ± 0.06	10.29± 0.06
Blood	10.19 ± 0.02	9.15 ± 0.09	4.9 ± 0.03	3.15 ± 0.09	1.90± 0.007	0.97 ± 0.006
Brain	9.55± 0.22	10.13 ±0.44	11.88± 0.19	6.13 ± 0.17	3.11 ± 0.09	2.10 ± 0.07
Liver	2.30 ±0.02	3.22± 0.02	3.29 ±0.03	4.15 ±0.03	3.99 ± 0.01	2.44 ± 0.06
Intestine	3.55± 0.01	3.65 ± 0.01	4.76± 0.08	3.19±0.02	2.33 ±0.007	2.12 ±0.002
Spleen	1.90 ± 0.003	1.88 ± 0.04	1.11 ±0.009	0.99± 0.001	0. 97± 0.001	0.96± 0.001
Stomach	1.11± 0.001	1.12± 0.002	0.99± 0.003	0.98±0.004	0.96±0.009	0.92±0.007
Heart	1.18 ± 0.005	1.19± 0.001	1.11± 0.007	0.99 ±0.00	0.98 ± 0.00	0.97 ± 0.00
Lungs	1.14 ± 0.001	1.15 ± 0.003	1.16± 0.001	1.17 ±0.004	1.11 ± 0.004	0.90 ± 0.00
Muscles	1.18 ± 0.01	1.27 ± 0.002	2.13± 0.04	3.18 ±0.009	2.40± 0.007	1.90 ± 0.006

Conflict of Interest

There is no conflict of interest associated with this publication.

Data Availability Statement

All the data were collected at Egyptian Atomic Energy Authority.

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