**ABSTRACT**

The present study was designed to investigate the effect of *Urtica dioica* plant parts "leaves and roots" separately, known as stinging nettle, on propionic acid (PPA) induced autistic like rat model on the behavior, monoamines and bioenergetics changes in rats compared with the synthetic drug risperidone. Sixty male albino rats were divided into 5 equal groups (n=12) and treated for 17 days as follows: 1- control {received (0.1M, PBS as 1ml/kg b.wt ip) and (0.5/100 w/v as 5ml/kg b.wt p.o) of carboxy methyl cellulose (CMC), 2- PPA received (250 mg/kg as 1 ml/kg b.wt; i.p) + CMC p.o. as control, group, 3- PPA+ RISP (1mg/kg b. wt, p.o), 4- PPA+ nettle leaves (NL, 50mg/kg b. wt, p.o) and 5- PPA+ nettle roots (NR, 50mg/kg b. wt, p.o). The three-box chamber and Y maze tests were performed from 15th to the 17th day. In the 18th day, rats were sacrificed and homogenates of cortical, hippocampal and midbrain tissues were used for the estimation of dopamine (DA), norepinephrine (NE) and serotonin (5-HT) contents along with the bioenergetics (ATP, ADP and AMP). The results showed that NR extract could attenuate behavior deficits together with the improvement of the monoaminergic system and bioenenrgetic. In contrast, NL extracts had a poor effect on behavioral improvement, monoamines levels and the bioenergetics. Therefore, it may be concluded that NR extract had a protective effect due to its impact on the behavioral, monoaminergic and bioenergetics systems.

**Keywords:** *Urtica dioica*, stinging nettle, propionic acid, risperidone, autistic disorder, mental retardation, behavioral improvement.

**INTRODUCTION**

Autism is a syndrome which is characterized by deficit in social interaction and repetitive behavior pattern caused by improper neuro-developmental process appear on children before 3 years of age. It is a spectrum multifaceted disorder. The prevalence of autism changes rapidly from 1 out of 10,000 children in the 1980's. But, in 2008, pervasiveness is 1 in every 88 children to the current statics 1 in 59 in 2018. The huge increase may be due to the border of criteria expanded in diagnosis of autism spectrum disorder (ASD) that is mainly neurobehavioral and also associated with much medical co-morbidity (Bjørklund et al., 2020).

Propionic acid (PPA), one of the main short chain fatty acids, plays particular role in the development, metabolism and immunity in health, but also in some inherited and acquired diseases, including those which affect brain function and behavior (Aguirre and Venema, 2017). High levels of PPA are accompanied by developmental delay, oxidative stress and metabolic or immune
disturbances, which have some similarities with propionic acidemias and autism (Nankova et al., 2014).

The genus *Urtica* is a member to the family Urticaceae in the major group Angiosperms (flowering plants). *Urtica* compounds are very important in medicine and pharmacology. For example, histamine has beneficial effect on the complex physiology of brain systems, affecting cognitive processes, including learning and memory (Blandin et al., 2004) most notably its inhibition of myeloid dendritic cells (Broer and Behnke, 2002), shows a protective impact against cerebral ischemia/reperfusion damage (Hornick et al., 2011), while modifying dopamine and serotonin concentration in the prefrontal cortex and hippocampus. *Urtica dioica* extract has been reported to improve spatial and associative memory dysfunction associated with chronic diabetes (Patel et al., 2015).

Risperidone acts on serotonin and dopamine and this makes it a choice to treat negative symptoms of schizophrenia and to reduce positive symptoms (Pajonk, 2004) and moderate autism behavior like quick mood change, self-injury, aggression toward others specially at low dose (Kirino, 2014).

The monoamine neurotransmitter including dopamine (DA), norepinephrine (NE), and serotonin (5-HT). Its main function is to keep brain normal development regulation movement, social communication, memory and general behavior (Choudhury et al., 2012). Based on these facts, neurotransmitters imbalance implicated in pathophysiology of autism (Chugani et al., 2001). NE major function is adapting to environmental change enhance flexibility and respond to emergent situation important in learning process (Sadacca et al., 2017). DA is inhibitory expiatory catecholamine and its main function is to regulate rewarding circuit that would be inhibited in autistic patient due to lack of communication in addition manage movement system (McNamara et al., 2014). Serotonin is a signaling molecule cross the body that mainly play a role in cell development generally (Celada et al., 2013) and specially neurons including proliferation, differentiation, migration, apoptosis synaptogenesis, neuronal and glial development alternation in serotonin distribution is linked to neuro-developmental disorder like diagnosis of autism spectrum disorder, ASD (Muller et al., 2016).

ASD is a grouped of metabolic disorders with multiple contribution to mitochondria dysfunction (MD) (Siddiqui et al., 2016) that were confirmed by a lot of researches and clinical investigations to individuals with ASD that considered MD a medical condition associated with it. Mitochondria is a powerhouse that provide cells with ATP. Especially, those that have a highly demand to energy like neurons (Zhu et al., 2012) contain many of it. Any disturbance in its function will affect directly the production of ATP. So measuring cellular bioenergetics (ATP, ADP, and AMP) can be a biomarker for mitochondrial disorders (Chacko et al., 2014 & 2019).

The aim of this work is to investigate the beneficial effect of *Urtica dioica* plant parts (leaves and roots) separately on the behavior; monoamine system and energy carriers in the brain of autistic like rat model induced by propionic acid and compared the obtained results with the synthetic drug used for treatment of ASD, risperidone.

**MATERIALS AND METHODS**

**Animals:**

A total of 60 young male rats weighed about 45-60 g (approximately 21 days old) were obtained from the animal house of Faculty of Pharmacy Mansoura University. Animals were housed in the animal house of Faculty of Science, Port-Said University. Rats were distributed randomly in standard cages (n= 6 per cage) to prevent over-crowding. The animal
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house maintained at 24°C and 50-60% relative humidity. A 12-hour dark/light cycle was maintained during the period. Rats had free access to food and water ad libitum. All experiments were performed according to the animal guidelines of Port-Said Faculty of Science and Ain Shams University.

Drugs:
Carboxy methylcellulose (CMC) was supplied as a white powder (Sigma Aldrich). Propionic acid was supplied as a solution (99.9% purity), purchased from Sigma (St. Louis, USA). The plant roots were supplied as herbal supplement capsules (500 mg/capsule), purchased from Swanson health product (USA). The plant leaves were supplied as herbal supplement capsules (200mg/capsule), purchased from Solgar, Inc, (NJ, U.S.A). Risperidone drug was supplied as tablets (4 mg), purchased from JANSSEN-CILAC.

Experimental design:
Sixty animals randomly divided into five groups (n=12), as follows:
1- Control group: received buffer phosphate saline 0.1 M as 1 ml/kg b.wt/day intraperitoneal and CMC (0.5 g /100 ml) as (5 ml/kg b.wt/day) by oral gavages injection daily through the experiment duration.
2- Propionic acid group: received PPA dissolved in 0.1 M Phosphate Buffered Saline and injected intra-peritoneally as 250 mg/kg (0.26 M, 1ml/kg b.wt/day) + CMC (0.5 g /100 ml) as (5 ml /kg) by oral gavages injection (Cloi et al., 2018).
3- Propionic acid + Risperidone drug group: received PPA at the same dose + Risperidone drug (1mg/kg b. wt/ day, as 5 ml /kg/ day po.) through the experiment duration.
4- Propionic acid + Nettle leaves extract group: received PPA with the same dose + Nettle leaves extract (50mg/kg) as (5ml /kg/day po.) by oral gavages daily through the experiment duration.
5- Propionic acid + Nettle roots extract group: received the same PPA dose + Nettle roots extract (50mg/kg) as (5ml /kg/ day po.) by oral gavages daily through the experiment duration.

Behavior analysis: the three box chamber and Y maze tests were performed in the days 15th, 16th, and 17th after one hour at least from the time of the daily injection. All the investigated groups were treated for 17 days then decapitated in the 18th day. The brain was removed on ice within 30seconds from the skull (Yashpal and Henry, 1984).

Three box-chamber sociability test:
The social test was performed in a three chambered apparatus as described by Nadler (2004); Ali and Elgholy (2013). The maze was obtained from Zoology Department of Women Faculty of Arts, Science and Education- Ain Shams University. It is a Plexiglass box with partitions separating the box into three chambers with dimensions (length/width/height in cm) 60/40/30. The openings between compartments allowed free exploration to the different chambers. Time spent in each chamber, as well as the time spent exploring the stranger rat or an object in the chamber, was analyzed. The object was an empty identical cage used to enclose the stranger rat. Chambers were cleaned with 70% ethanol and water between tests. Animals used as “strangers” were males with the same age“21 days” and no previous contact with the test rats. For the sociability test, rats allowed expending 10 min in the central chamber, and then the stranger rat was introduced into one of the side chambers. The experiment was performed for up to 10 min, with the stranger rat and an object on each side. The three chambered apparatus was centered on a lab bench to minimize light gradients in temperature, sound and
other environmental conditions that could produce a side preference. The number of entries was recorded when the four limbs of the rat passed the gate of the chamber.

Y maze: comprises of a capital Y-shape, with three arms marked A, B, and C. The point between the arms is 120°; every division of the maze is 40 X 15 X 30 cm, long X wide X high individually (Roghani et al., 2006). The floor and sides of each arm are made of wood. The maze utilized to evaluate spontaneous alternation. Each rodent was placed in one of the arms (arm A) confronting the focal point of the maze and allowed to move freely among the three segments for 5 min. The absolute number of arm passages was recorded by an advanced camera to assess the locomotion. A passage was possibly recorded if each of the four appendages were set into the arm. The all out number of arms entered gives a sign of locomotion activity, and the request for arms entered gives a proportion of spontaneous alternation and in this way assess working memory and stereotypic conduct. The maximum spontaneous alternations is determined as the spontaneous alternation X 5 less two, the correct alternation is determined as the progressive passages into the diverse three arms on covering triplet sets (i.e., ABC, CBA, BAC), the percentage alternation is calculated as \{(actual alternations/maximum alternations) x 100\}, and the percentage of correct alternation is calculated as \{(correct alternation/maximum alternations) x 100\}. The maze was cleaned with 70% alcohol and allowed to dry between sessions (Roghani et al., 2006; Hegazy et al., 2016).

Biochemical analysis:
Each brain of 6 different individuals per group was kept frozen for the biochemical investigation. The brain tissues were extracted on the ice at room temperature and dissected to obtain the frontal cortex, midbrain and the hippocampus from each brain. The obtained tissues were grinded well by using the manual grinder at potassium phosphate buffer (PBS; 7.2 PH) as 10% weight/volume of tissue homogenate buffer, i.e. (0.7 mg brain tissue in 7 ml buffer). Then spin at 2000Xg for 2 min to partially clarify and separate the aqueous layer from supernatant then kept in -20°C for the biochemical investigations.

Estimation of the brain catecholamines (cortex, midbrain and hippocampus):
The Agilent HPLC system used with Rheodyne injector 20μl loop and an ultraviolet (UV) variable wavelength detector was used for monoamine assays where the samples were injected directly into an AQUA column C18, purchased from Phenomenex, the USA under the following conditions: mobile phase 97/3 from 20Mm potassium phosphate, pH 3.0/ methanol, flow rate 1.5ml/min, UV 270 nm. NE, DA, and 5-HT were separated after 10 minutes. The obtained chromatogram identified each monoamine position and concentration from the sample as compared to that of the standard, and finally, the calculation of the content of each monoamine as µg per gram brain tissue was made according to Pagel et al. (2000).

Measurements of energy carrier's molecules:
The detection of AMP, ADP, and ATP by HPLC was done according to the method of Liu et al. (2006). Two hundred microliters of samples (supernatant of brain tissue) was added to 1ml of 70% methanol for deprotonization. The samples were centrifuged at 4500 rpm for 5 min and used for HPLC analysis. Samples were eluted isocratically and analyzed on C-18 Spherclone column, mobile phase divided into A, B Where: A→ (0.04 M monobasic potassium phosphate, pH=5.5), B→ (0.5 M monobasic potassium phosphate, pH=5.5), A/B: 100 / 0 in 26 min A/B reach to 0 /100, within flow rate (1ml/min),
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cromatographic determination was performed on Perkin–Elmer HPLC. The report and chromatograms were taken from data acquisition program purchased from Perkin–Elmer at wave length 254 nm and injection volume 20 µl.

**Statistical analysis:**
Values are means ± standard error of 6 animals for biochemical analysis and 12 animals for behavior tests. Analysis of variance (ANOVA) was performed using a Statistical Package for Social Science (SPSS, V.23, USA). Once a significant F value was obtained, post hoc LSD test was performed using the same program.

**RESULTS**
By estimating the cortex norepinephrine (COR-NE) values, it was noticed a high significant (P < 0.001) depletion in COR-NE contents of the PPA, PPA+RISP and PPA+NL treated groups as compared with the CON group. On the other hand, PPA+NR treated group exhibited a high significant (P < 0.001) increase in COR-NE contents in comparison with the PPA treated groups. Moreover, a significant (P < 0.05) decrease in hippocampus norepinephrine (H-NE) in PPA+RISP, PPA+NL, and PPA+NR treated groups in comparison with the CON group was observed. Also, the PPA+NR, PPA+NL groups showed a high significant (P < 0.001) reduction in the midbrain norepinephrine (Mb-NE) value when compared with the CON group. As well as, PPA, PPA+RISP treatment induced significant (P < 0.01) decrease in the Mb-NE contents when compared with the CON group as shown in Table (1).

The recorded values of COR-DA contents revealed that the PPA, and PPA+NL treated groups showed a high significant (P < 0.001) depletion as compared with the CON group. Also, PPA+NR group exhibited a significant (P < 0.01) decrease in COR-DA content as compared with the CON group (Table 1). While, the PPA+RISP treated group showed a high significant (P< 0.001) increase in the COR-DA values when compared to the PPA treated group. The PPA+NR treatment caused a significant (P < 0.01) increase in COR-DA as compared to the PPA treatment.

The result of measuring dopamine in the hippocampus indicated that the PPA+NR treated group has a high significant (P < 0.001) decrease when compared to the CON group. Moreover, the PPA+NL treated group exhibited a significant (P < 0.01) diminution in the value of H-DA when compared to the CON group. Also, the PPA treated group showed a significant (P < 0.05) decrease in the value of H-DA when compared to the CON group. In contrast, the PPA+RISP treatment induced a significant (P < 0.05) increase in H-DA values as compared to the PPA treatment. While, the PPA+NR treated group exhibited a significant (P < 0.01) depletion in the level of H-DA when compared to the PPA treated group. Data showed that the PPA, PPA+RISP, PPA+NL, and PPA+NR treated groups exhibited a high significant (P < 0.001) depletion in Mb-DA contents as compared to the CON group. While, PPA+NL treated group revealed a significant increase (P < 0.01) in Mb-DA contents as compared with the PPA group.

Data in Table (1) showed that the PPA and PPA+NL treatment induced a high significant (P < 0.001) reduction in the COR-5HT contents when compared with the CON group. Also, the PPA+RISP, and PPA+NR treatment caused a significant (P< 0.05) decrease in the COR-5HT contents when compared with the CON group. However, high significant (P < 0.001) elevations in COR-5HT contents were induced by PPA+NR, PPA+RISP treatment when compared with the PPA treatment. However, the PPA, PPA+RISP and PPA+NL treated groups showed a statistically but not significantly change in
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the level of H-5HT when compared to the CON group. Moreover, no significant change was noticed in PPA+RISP or PPA+NL in the level of H-5HT in comparison with the PPA treated group. While, PPA+NR treated group displayed a significant (P < 0.05) depletion in the level of H-5HT when compared to the CON group. Also, it showed a significant decrease (P < 0.01) when compared to the PPA treated group. A high significant (P < 0.001) decrease in the Mb-5HT contents were observed in the PPA, PPA+RISP and PPA+NL treated groups when compared with the CON group. Also, there was a significant (P < 0.05) reduction in the PPA+NR group in the Mb-5HT contents as compared to the CON. A significant (P < 0.05) increase was shown in Mb-5HT contents in PPA+NR treated rats as compared to the propionic acid treated group.

Table (1) : Effect of different treatments by stinging nettle leaves (NL), roots (NR) and risperidone (RISP) drug on monoamine (norepinephrine (NE), Dopamine (DA), serotonin (5-HT)) contents (ug/g wet tissues) in the cortex, hippocampus and midbrain of rats induced by propionic acid (PPA).

| Groups | Cortex | Hippocampus | Midbrain |
|-------|--------|-------------|----------|
| CON   | 0.72±0.027 | 0.47±0.024 | 0.51±0.017 |
| PPA   | 0.52±0.021 a*** | 0.4±0.026 | 0.40±0.015 a** |
| PPA+RISP | 0.55±0.015 a*** | 0.38±0.023 a* | 0.39±0.026 a** |
| PPA+NL | 0.47±0.02 a*** c* | 0.38±0.040 a* | 0.37±0.017 a*** |
| PPA+NR | 0.67±0.014 b** c**** d**** | 0.37±0.009 a* | 0.37±0.031 a*** |
| CON   | 1.7±0.044 | 1.1 ±0.048 | 1.3±0.048 |
| PPA   | 1.2±0.0395 a*** | 0.96±0.043 a* | 0.78±0.034 a*** |
| PPA+RISP | 1.6±0.052 b*** | 1.1 ±0.022b* | 0.87±0.004 a*** |
| PPA+NL | 1.1±0.034 a*** c*** | 0.92±0.025 a*** c** | 0.96±0.068 a*** b** |
| PPA+NR | 1.4±0.079 a** b** d*** | 0.81±0.027 c*** | 0.85±0.043 a*** |

| Groups | Cortex | Hippocampus | Midbrain |
|-------|--------|-------------|----------|
| CON   | 0.75±0.019 | 0.43±0.027 | 0.54±0.034 |
| PPA   | 0.47±0.032 a*** | 0.44±0.029 | 0.37±0.027 a*** |
| PPA+RISP | 0.68±0.025 a*b*** | 0.38±0.013 | 0.39±0.019 a*** |
| PPA+NL | 0.47±0.018 a*** c*** | 0.44±0.023 | 0.34±0.013 a*** |
| PPA+NR | 0.66±0.029 a** b** c*** | 0.34±0.028 a** b** d*** | 0.46±0.014 a*** |

Values are means± SE of six rats, a=significant difference compared with control group(CON), b=significant difference compared with propionic acid group (PPA), c=significant difference compared with propionic acid + Risperidone treatment group(PPA+RISP), d=significant difference compared with propionic acid + nettle leaves treatment group(PPA+NL), *Significant level of probability (P<0.05), ** Significant level of probability (P < 0.01), *** Significant level of probability (P <0.001), Non-significance (P ≥0.05).

It was obvious from data in Table (2) that the PPA, PPA+RISP, PPA+NL and PPA+NR treatments induced a great significant depletion (P < 0.001) in the concentration of COR-ATP when compared to the control group. Moreover, PPA+RISP and PPA+NR groups exhibited a significant increase (P < 0.01) in the
COR-ATP content in comparison with the control or PPA group. But a high significant decrease (P < 0.001) was observed in the PPA+NR when compared to the control and PPA treated groups. Moreover, all the treated groups showed a high significant decrease (P < 0.001) in the level of Mb-ATP as compared to the control group. But, the PPA, PPA+RISP and PPA+NL treated groups showed a statistically but not significantly increase in the Mb-ATP when compared to the PPA group.

Table (2): Effect of different treatments by stinging nettle leaves (NL), roots (NR) and risperidone (RISP) drug on bioenergetics (adenosinetriphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP)) contents (ug/g wet tissues) in the Cortex, hippocampus and midbrain of rats induced by propionic acid (PPA).

| Groups     | Cortex     | hippocampus | midbrain  |
|------------|------------|-------------|-----------|
| Control (CON) | 43.8±0.68  | 25.4±0.420  | 31.4±0.210 |
| PPA        | 31.8±1.06  a*** | 25.8±0.728  | 23.8±0.515 a*** |
| PPA+RISP   | 37±0.99    a***b** | 25.02±0.572 | 23.3±0.999 a*** |
| PPA+NL     | 28.3±1.68a***b*c*** | 24.5±1.13 | 24.2±0.927 a*** |
| PPA+NR     | 36.6±0.45a***b***d*** | 20.3±0.763 a***b***c***d*** | 21.8±0.870 a***d* |

| Groups     | Cortex | hippocampus | midbrain |
|------------|--------|-------------|----------|
| CON        | 24.7±0.332 | 15.2±0.610 | 19.6±0.118 |
| PPA        | 18.5±0.36a*** | 15.5±0.448 | 14.0±0.796 a*** |
| PPA+RISP   | 23.6±0.84 b**** | 15.9±0.679 | 13.4±0.408 a*** |
| PPA+NL     | 16.3±0.8 a***b*c*** | 15.7±0.877 | 13.8±0.665 a*** |
| PPA+NR     | 22.7±0.54 a**b***d*** | 11.4±0.277 a***b***c***d*** | 14.4±0.0542 a*** |

| Groups     | Cortex | hippocampus | midbrain |
|------------|--------|-------------|----------|
| CON        | 15.8 ±0.422 | 9.1 ±0.099 | 9.3±0.491 |
| PPA        | 9.7±0.642 a*** | 7.8±0.386 a* | 6.8±0.306 a** |
| PPA+RISP   | 12±0.781 a***b* | 7.2±0.568 a** | 7.7±0.494 a* |
| PPA+NL     | 9.9±0.608 a***c* | 7.3±0.214 a** | 7.3±0.629 a* |
| PPA+NR     | 11.8±0.780 a***b* | 6.3±0.374 a***b** | 6.8±0.596 a** |

Values are means± SE of six rats, a=significant difference compared with control group (CON), b= significant difference compared with propionic acid group (PPA), c=significant difference compared with propionic acid + Risperidone treatment group (PPA+RISP), d= significant difference compared with propionic acid + nettle leaves treatment group (PPA+NL), propionic acid +nettle roots (PPA+NR), *Significant level of probability (P<0.05), ** Significant level of probability (P < 0.01), *** Significant level of probability (P <0.001), Non-significance (P ≥0.05).

Table (2) indicated the presence of a significant decrease (P < 0.001) in the content of COR-ADP of the PPA administrated group and the PPA+NL treated group when compared to the CON group. Also, a significant
decrease (P < 0.05) was shown in COR-ADP contents in the PPA+NR treated group when compared to the CON group. On the other hand, the PPA+ RISP, and PPA+NR groups exhibited a high significant elevation (P < 0.001) in the level of COR-ADP when compared to the PPA group. Analyzing data in Table (2) indicated that there was no significant remarked in the PPA, PPA+RISP and PPA+NL treated groups when compared to the control group and the PPA group. On other hand, there was a high significant depletion (P < 0.001) in the level of H-ADP in PPA+NR when compared to the CON and PPA treated groups. Moreover, there was a high significant decrease (P < 0.001) in Mb-ADP in all treated group when compared to the CON group.

Recorded value estimated that there was a great significant diminution (P < 0.001) in the COR-AMP level of PPA, PPA+NL, PPA+ RISP and PPA+ NR treated groups as compared to the CON group. While, a significant (P < 0.05) increase was noticed in the PPA+RISP, and PPA+NR treated when compared to the PPA group. Also, the PPA+NR showed a high significant decrease (P < 0.001) in the H-AMP contents as compared to the CON group. Moreover, the PPA+RISP, and PPA+NL exhibited a significant (P < 0.01) decrease in the level of H-AMP when compared to the CON group. However, the PPA group showed a significant (P < 0.05) decrease in the level of H-AMP when compared to the CON group. Also, PPA+NR group exhibited a significant decrease (P < 0.01) in H-AMP when compared to the PPA group.

Regarding midbrain, there was a significant decrease (P < 0.01) in the Mb-AMP contents when compared to the CON group. Also, the PPA+RISP and PPA+NL treated group exhibited a significant decrease (P < 0.05) in the Mb-AMP contents when compared to the CON group. On other side, the PPA+RISP, PPA+NL, PPA+NR treated groups showed a statistically but not significantly increase in the level of Mb-AMP when compared to the CON group.

Regarding the three-box chamber, data in Figure (1) showed that the PPA, PPA+NL and PPA+NR treated groups exhibited a high significant decrease (P < 0.001) in the number of entries when compared to the CON group. Also, the PPA+RISP treated group exhibited a significant decrease (P < 0.01) in the number of entries when compared to the CON group.

![Fig. (1): Effect of different treatments stinging nettle (leaves(NL), roots(NR) and risperidone (RISP) drug on the number of entries to the chambers per ten minutes (a); the sociability preference in different treated groups represented by time spent in three box chamber maze (b).](image)

Values are means± SE of 12 rats, a=significant difference compared with control group(CON), b=significant difference compared with propionic acid group (PPA), c=significant difference compared with propionic acid group, Risperdone treatment group (PPA+RISP), d= significant difference compared with propionic acid + nettle leaves treatment group(PPA+NL), propionic acid +nettle roots (PPA+NR). *Significant level of probability (P<0.05), ** Significant level of probability (P < 0.01), *** Significant level of probability (P <0.001), Non-significance (P ≥0.05).
In contrast, the PPA+RISP and PPA+NR treated groups showed a significant (P < 0.05) increase in the number of entries in comparison with the PPA group. Moreover, all the treated groups exhibited a high significant (P < 0.001) decrease in the time spent in the left-side with the stranger when compared to the CON group. However, the PPA+RISP and PPA+NR treated groups showed a significant (P < 0.001) increase in the time spent in the left-stranger side when compared to the PPA group. In contrast, the PPA and PPA+NL treated groups exhibited a statistically but not significantly change in the time spent in the middle chamber when compared to the CON group. While, the PPA+RISP and PPA+NR treatment induced a significant (P < 0.001) decrease in the time spent in the middle when compared to the CON and PPA treated groups.

Regarding the time spent in the right-empty side, the PPA, PPA+RISP, PPA+NL and PPA+NR treatments caused a high significant (P < 0.001) increase when compared to the CON group. While, the PPA+RISP and PPA+NR treated groups exhibited a significant (P < 0.01) decrease in the time spent in the right-empty side when compared to the PPA group. Also, PPA+NL showed a significant (P < 0.05) decrease in the time spent in the right-empty side in comparison with the PPA group. The stereotype activities and memory were assessed through the number of alternation and the number of correct alternation and they percentage in Y maze as shown in Figure (2). Data showed that all the treated groups exhibited a high significant (P < 0.001) decrease in the number of arm entries when compared to the CON group. While, the PPA+RISP and PPA+NR treated groups showed a significant (P < 0.001) increase in the number of arm entries when compared to the PPA group. Moreover, all the treated groups exhibited a high significant (P < 0.001) decrease in the number of correct alternations when compared to CON group. In contrast, the PPA+RISP and PPA+NR treatment induced a significant (P < 0.001) increase in the number correct alternations when compared to the PPA group. While, the PPA, PPA+NL treatments caused a significant (P < 0.001) increase in the percentage of alternations when compared to the CON group. In contrast, the PPA+NR and PPA+NR treated groups showed a statistically but not significantly increase in the percentage of alternations when compared to the CON group. Also, the PPA+RISP and PPA+NR treatment induced a significant (P < 0.001) decrease in the percentage of alternations as compared to the PPA group. While all the treated groups showed a statistically but not significantly increase in the percentage of correct alternations in comparison with CON and PPA groups.

Fig.(2): Effect of treatment with Urtica dioica (roots and leaves) extracts and the risperidone drugs on the rat performance in Y-maze number of arm entries/ 5 min and correct alternations (a) and percentage of alternation and correct alternations (b) of the control and different treated groups.

Values are means± SE of 12 rats, a=significant difference compared with control group(CON), b= significant difference compared with propionic acid group (PPA), c=significant difference compared with propionic acid + Risperidone treatment group(PPA+RISP), d= significant difference compared with propionic acid + nettle leaves treatment group(PPA+NL), propionic acid +nettle roots (PPA+NR), *Significant level of probability(P<0.05), ** Significant level of probability (P < 0.01), *** Significant level of probability (P <0.001), Non-significance (P ≥0.05).
DISCUSSION

The present data revealed that the systematic treatment with PPA produced a significant reduction in the three monoamines in the cortex and midbrain but, in hippocampus reduction occurs in dopamine only when compared to the control group. The present findings agreed with Nankova et al. (2014); Al-Salem et al. (2016); Shams et al. (2019). They reported that treatment of propionic acid reduced monoamines in the brain tissues. This may be due to the effect of PPA on tyrosine hydroxylase enzyme (Decastro et al., 2005) which is like the action of butyrate short chain fatty acids that have the property to alter tyrosine hydroxylase gene expression. Tyrosine hydroxylase (TH) enzyme is responsible for monoamine biosynthesis transmitter and propionic acid may decrease it via reduce histone acetylation (Liu et al., 2014).

Meyer et al. (2006) gave another explanation for the action of PPA on brain monoamine neurotransmitters, where it elevates monoamine oxidase A (MAO-A) activity in the brain which causes the depletion. Therefore, the inhibition of MAO-A activity could prevent the breakdown of monoamine neurotransmitters and contribute to the increase of neurotransmitters in the synaptic cleft (Béroule, 2018).

Deficiency in neuromodulator enzymes may be due to MOA-A gene which shows allelic variant property that reflects variation in function. Deckert et al. (1999) mentioned that if MOA-A gene contains three repeated allele, it will show low action but when contains the repeated allele number four it turns its opposite main function. This explains the deficiency of this enzyme among autistic children. Interestingly, it is very sensitive to environmental change (Meyer et al., 2009) and start to increase in brain at childhood age (2 to 4) in the same time when autism symptoms start to appear.

Miller and Timmie (2009) indicated that the elevation of cytokines in brain cells disrupt the synthesis and the reuptake of monoamine neurotransmitters. Two mechanisms prove these hypotheses the first mechanism including administration of cytokines to animals which influence monoamine neurotransmitter metabolism (Felger et al., 2007; Anisman et al., 2008). The second mechanism drugs that affect monoamine metabolism produced cytokines in brain cells (Bull et al., 2008). Induction of cytokines such as IL6 which increase as a result of injection PPA (Mac Fabe et al., 2011) produce indolamine 2, 3-dioxygenase (IDO) enzyme (Fujigaki et al., 2006) that have the capacity to lysis the amino acid tryptophan precursor of serotonin into kynurenine that converted to kynurenic acid in astrocytes and microglia which will inhibit the production of 5-HT (Dantzer et al., 2008). Kynurenic acid inhibits the release of glutamate which lead to inhibition of dopamine whose release in a part of glutamateric activity (Borland and Michael, 2004).

Nitricoxide (NO) elevation is associated with injection of PPA affecting the dopamine synthesis (Kitagami et al., 2003). Accumulation of NO inside the cell occur by the action of BH4 enzyme cofactor (tetrahydrobiopterin) which is also have a curial role in the synthesis of dopamine via hydroxylation of tyrosine into L-3,4-dihydroxyphenylalanine (LDOPA) and is the rate-limiting enzyme in DA synthesis.

Dopamine role in the cortex is responsible for behavior flexibility and cognitive control (Naneix et al., 2009). Increase or decrease in dopamine content can alter its main function (Del Campo et al., 2011; Ali and Elgoly, 2013; Hegazy et al., 2015). Reduction of DA and NE is associated with attention-deficit hyperactivity disorder that linked to the
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decrease in cortex activity (Zhang et al., 2017). Dopaminergic loss is a pivotal pathophysiology mechanism, giving rise to cortico-striatal dysfunction, i.e. indirect pathway overactivity and direct pathway hypoactivity. It has also been revealed that different degrees of dopaminergic loss exert contrasting effects on the maintenance of two distinct types of cortico-striatal synaptic plasticity, in the medium spiny neurons of the striatum (MSN). In particular, the cortico-striatal long-term depression in MSNs is not altered by incomplete (approx. 75%) dopamine depletion, whereas the cortico-striatal is critically affected (Moghaddam et al., 2017).

Microglial over-activation has also been implicated as a potential felon mediating mood symptom via decreasing monoamines during elevated levels of inflammatory cytokines. More specifically, TNF-α and IL-1β are potent activators of microglia as part of the innate immune system (Harry and Kraft, 2012). Microglia over activation may associated with over-pruning of neural circuits, reduce neuroplasticity and ultimately disfunction of the neuronal circuits leading to impaired cognition and emotional regulation on a functional level (Rosenblat et al., 2014). Further, microglia activation impairs glutamate metabolism leading to alteration of glutamate levels and glutamate receptor activation (Hashimoto et al., 2013).

Regarding RISP, in the present study there was an increase in the content of DA and 5-HT, however a statistically but not significantly difference was noticed in the content of NE in cortex tissues when compared to the PPA group. Moreover, RISP showed a significant increase in dopamine value only in hippocampus when compared to the PPA group. Although, our data revealed no effect of RISP on midbrain monoamines as compared to PPA group. These results could explain by the effect of RISP on DA receptors which depend on the dose (Moran-Gates et al., 2007). Our results in cortex cells explain the action of RISP as a blocker to α1 5-HTA2 and α2D2 receptors (Aghajanian and Marek, 2000). The present results are in consistent with Kaminiska et al. (2018), Del Acro and Mora (2008), Ichikawa et al. (1998), (Meltzer et al. (2002) who found that RISP raise the level of DA more than the level of 5-HT and suggested that RISP was blocking the presynaptic D3 receptor hence elevated DA neural terminal via partial working on antagonistic 5-HT1A receptors and weak antagonist at 5-HT2c receptors. Increase in the level of DA is due to the action of RISP on the 5-HT1A receptors agonists which mediate indirectly through GABAergic in VAT suppressing these interneurons (Wedzony et al., 1996). This may explain the present result in hippocampus which showed elevation in DA only, so RISP has a high affinity for 5-HT2A receptors by blocking all that located on GABAergic interneurons in the frontal cortex. Elevation in the level of 5-HT may be due to disinhibition of glutamatergic efferent pathway that also lead to DA release from raphe nuclei (Santana et al., 2004).

Elevation of dopamine only in hippocampus in the present work may be due to the action of RISP to elevate DA is greater than 5-HT. Dopamine is the only monoamine that decrease in the PPA treated rats in this area. But monoamines in midbrain have not statically increase when compared to the PPA treated rats because its area of synthesis is not affected by RISP. It mainly works as blocker to receptors in cortex and cause neurodegenerative (loss in dopamine neuron) in midbrain area by reduce tyrosine hydroxylase enzyme (Reynolds et al., 2011).

As for NL extract and NR extract, the results revealed that NL extract has poor effect on the brain monoamines except its elevated DA in midbrain when compared to the PPA group. That’s may
be due to nettle leaves contain 5% of alkaloids (Skalozubova and Reshetova, 2013). It works as monoamine oxidase-A inhibitor (Zhang et al., 2018) and a MOA-B inhibitor (Mazzio et al., 2013). Enzymes work together and very important in catabolism of dopamine and its precursor like phenylalanine, tyrosine and tryptamine (Kaluganov et al., 2001) which lead to decrease in dopamine. But inhibitor enzymes prevent catabolism which lead to increase in dopamine. Alkaloids results in the interaction with the Paired Associative Stimulation (PAS) of AChE, especially with Trp279 of PAS (Tang et al., 2009) which leads to an increase of the acetylcholine level and improved learning and memory abilities. Pharmacological effect that combines enhancement of cholinergic neurotransmission with a decrease in the pro-aggregating action of AChE (Zhang et al., 2018).

On the contrary, NR extract revealed a significant effect on monoaminergic system on NE, DA and 5-HT in cortex, and 5-HT in midbrain. These results could explain by the neuroprotective effect of UD. it can raise the content of DA and 5-HT in prefrontal cortex according to Hornick et al. (2011). It contains 5-HT precursor like 5-hydroxytryptamine, acetylcholine, choline, acetyltransferase and serotonin (Nahata and Dixit 2014 and Patel et al., 2016). Also, a possible explanation to nettle root effect on monoamine in our results was shown by Bisht et al. (2016). Inhibition of the MAO activity is very important in upregulating the levels of neuroactive amine such as dopamine, serotonin, and norepinephrine in the brain (Ademosun et al., 2016).

_Urtica dioica_ contains flavonoids (Akbay et al., 2003) and phenolics (Ioana et al., 2013), flavonol glycosides (kaemferol-3-O-glucoside and -3-O-rutinoside; quercetin-3-O-glucoside and –3-Orutinoside; isorhamentin-3-O-glucoside; –3-O-rutinoside; and –3-oneohesperidoside (Chaurasia and Wichtl, 1987), some of which are major contributors in the antioxidant activity of _Urtica dioica_. Extract of nettle ( _U. dioica_ ) has been recently indicated to show free radical scavenging activity (Ghaima et al., 2013). The HPLC analysis showed the presence of a bioactive marker, like ferulic acid which was reported to be a phenolic compound (Bisht et al., 2016) that have a neuroprotective effect (Hassanzadeh et al., 2018). Plants containing polyphenolic compounds have been reported to inhibit MAO activity (Oboh et al., 2016). There is a strong correlation between total phenolic content and biological activities (Aliyazicioglu et al., 2013; Oboh et al., 2017). This result revealed that phenolic compound may play an important role in the treatment of neurological disorders associated with depression and could prevent neurodegeneration in autism patients due to the structural similarities between phenolic compounds and synthetic inhibitors of these enzymes especially their hydrophobic component and phenolic rings (Benamar et al., 2010 and Nebbioso et al., 2012). Many natural effective antioxidant compounds such as flavonoids, phenolics, and polyphenols have neuroprotective role in various nervous system disorders by reducing oxidative stress induced mitochondrial dysfunction by decreasing the production of Bax and Bad protein, favoring an increase in the Bcl2–BclX/L/Bax–Bak ratio (Mandel and Youdim, 2004).

The present data revealed that injection of PPA to the rats caused a decrease in bioenergetics (ATP, ADP and AMP) in cortex and midbrain but depletion occur in AMP in hippocampus when compared to the control group. Frye et al. (2016) measured ATP in the cell line PC_{12} and they found that at normal physiological condition with optimal dose of PPA, it shows a benefit role in mitochondria metabolism. Even if mitochondria expose to high dose of PPA with a continuous period it still beneficiable by act as a fuel increasing level of ATP,
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the final product of its metabolism up to 48 hours only. However, a reduction reported in the level of ATP due to a higher concentration and long period is trigger ROS (Villar et al., 2013) by PPA which metabolized to propionyl-CoA that access the CAC as succinyl-CoA. At physiological concentrations, this adds substrates to the CAC and boost mitochondrial function. However, high levels of succinyl-CoA, especially for a prolonged period of time, can inhibit CAC enzymes and over utilize acetyl-CoA, both of which might result in mitochondrial dysfunction, presumably by reducing the production of nicotinamide adenine dinucleotide, resulting in a decrease in ETC complex I function (Frye et al., 2015; 2016).

RNS, when present, can react with PPA to produce 3NP, a compound that strongly inhibits mitochondrial function through irreversible inhibition of succinate dehydrogenase (Francis et al., 2013). Inhibition of succinate dehydrogenase shuts down the CAC from the succinate onward. Beneficial effects have been seen in brain after treatment with allopurinol or febuxostat to inhibit xanthine oxidoreductase, which catalyzes hypoxanthine (Johnson et al., 2019).

Regarding RISP the present result illustrated reduction in the three bioenergetics in cortex when compared to the control group while, showed a significant increase in the three bioenergetics when compared to the PPA group. In hippocampus decrease in AMP when compared to the control group. While, no change in the level of bioenergetics when compared to the PPA group Moreover, in midbrain decrease in all bioenergetics when compared to PPA group and control group. The current result agreed with the results of Liddle et al. (2000) and Lane et al. (2004). Reduction in bioenergetics in different area is related risperidone extra-pyramidal side effects.

The NL showed no change in the three bioenergetics in cortex, hippocampus and midbrain when compared to the PPA group. While, the NR groups exhibited a significant increase in the three bioenergetics in the cortex tissues, but a decrease was shown in hippocampus with no change in midbrain when compared to PPA group. Nettle root restoration of the bioenergetics levels may explain by the feluric acid (FA) which is one of the main components of NR (Bisht et al., 2016). Recent research suggested that FA can regulate CAC circulatory dysfunction by increasing the ATP level in the limbic area of the brain of mice via activation of genes related to energy metabolism (Sasaki et al., 2019) and the action of NR to decrease NO and MDA and proinflammatory cytokines that may be help in regulation of mitochondrial functions (Bisht et al., 2016; Ghasemi et al., 2019).

Previous studies have been outlined that propionic autistic like rat's model exhibited autism-like symptoms especially social defect which is the most characteristics' related to autism (Mirza and Sharma, 2018; Shams et al., 2019). Similar results were obtained in the current study, where analysis of social behavior test using three box chamber apparatus revealed that PPA-treated rats showed defect in social behaviors when compared to the control group that including the time spent with the stranger who significantly lower in PPA treated rats than control group. The possible mechanism behind that behavior was that DA and 5-HT neurotransmission in the meso-corticolimbic pathways control social behaviors and social cognition of humans and animals (Kiser et al., 2012). In human studies, both decrease and increase of 5-HT and DA transmission signals such as 5-HT metabolite depletion and SSRI treatments which implicated in social defect (Rot et al., 2006).

The present data revealed a decrease in the content of serotonin and
dopamine in cortex of PPA treated rat when compared to control which explain the behavior defect. The ventral tegmental area and the substantia nigra two dopaminergic neurons groups that projected from midbrain may be implicated in controlling behavior (Haber et al., 2015). For social defect behavior, the decreased dopamine in mesocortico-limbic (MCL) circuit cause (MCL) dysfunction which will lead to decrease dopamine in the prefrontal cortex. These results were confirmed by our result for cortex dopamine contents in PPA treated rats. This decrease in COR-DA could alter reward and motivation and decision-making interaction which impacts social cognition which lead to social deficits (Chevallier et al., 2012). Also, social defected animal is characterized by low ATP (Liu et al., 2017). These results were confirmed by great reduction of bioenergetics (ATP, ADP and AMP) in different brain area (cortex, hippocampus and midbrain) of PPA treated rat when compared to the CON group as shown in the present work.

RISP could modify the social behavior defect produced by PPA due to its profile as a 5-HT2 antagonist, since these serotonergic receptors have been related to social interaction behavior (File and Seth, 2003). This was clear in increasing the time spent exploring stranger rat in three box chamber maze. Treatment with risperidone decreased aggressive behavior (Moechars et al., 1998). It also corrects the aggression induced by social isolation in male mice (Uchida et al., 2009) and the attack behavior in male albino mice (Rodríguez-Arias et al., 1998). Risperidone has also been found to enhance pro social behavior in children with disruptive behavior and sub-average IQ (Snyder et al., 2002). Recent findings have shown that atypical antipsychotic treatment enhances the gene expression of oxytocin which is associated with the promotion of interpersonal trust (Keri et al., 2009). The cognitive behavioral mechanism of how atypical antipsychotic treatment improves social relationships remains unclear. Together, we postulate that atypical antipsychotic treatment, lowering the transmission of 5HT2A receptor, may effectively increase interpersonal trust and lead to improvement in social behavior.

The present investigation results indicated that NL has a poor effect in animal performance in social interaction test, and there was no change in the time spent with stranger when compared to PPA group. On contrast, it increased the time spent in the empty room with no increase in monoamine neurotransmitter or bioenergetics and increased pro inflammatory cytokines that has a negative effect in emotion and social behavior in animals. On the other hand, NR decreased the time spent in the empty room and increased the time spent with stranger which mean enhance social interaction of animal that was altered by PPA. This may be due to NR increases DA, and 5-HT and reduces NO and MDA and increases bioenergetics and reduces Pro-inflammatory cytokines that implicated in impaired social interaction (Ghasemi et al., 2019).

The current results for PPA treated rat showed a reduction in spontaneous alt and the percent of correct alt in Y maze task when compared to control group. This result agreed with Mirza and Sharma (2018) which reflected short memory loss and abnormal behavior related to repetitive behavior. Stereotypic behavior may result from dopamine reduction in midbrain through dysfunctional nigro-striatal-cortical pathway neuronal circuit involved in cognitive processes such as spatial working memory. Many of the autistic children behavior insists in routines, they refuse change a known path (Mirenda et al., 2010). That a second typical symptoms of ASD is repetitive and restricted behaviors (Moy et al., 2008) which may be due to DA or 5-HT decrease in the hippocampus and midbrain. It has been
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reported that depletion of 5-HT in the brain produces an impairment of short-term memory but not of long-term memory (Hritcu et al., 2007) especially depletion of prefrontal 5-HT (Clarke et al., 2004) and inhibitory effect of 5-HT on other neurotransmitters involved in this process, such as norepinephrine and acetylcholine (Bell et al., 2001). Such inhibition could facilitate the acquisition of information within short-term memory (Masaki et al., 2006). Like any other neurotransmitter, the activity of 5-HT is mediated by specific receptors. Accordingly, the synaptic and physiological effects of serotonergic synapses depend on the type of receptor that is stimulated in the synapse. Likewise, these synapses can also be influenced by possible interactions between these serotonergic terminals and other neurotransmitter systems such as the cholinergic system in the hippocampus, cortex and striatum, where both systems cooperate in the regulation of cognitive functions. The 5HT1A receptors are closely associated with learning and memory (Meneses and Perez-Garcia, 2007). Transmission mediated by 1A receptors in the raphe complex, amygdala, septum, hippocampus and cerebral cortex, in relation to cognitive processes (Meneses, 2015). The 5HT1A receptors are present in 60% of the prefrontal pyramidal neurons and in 25% of the GABAergic interneurons (Santana et al., 2004). Like 5-HT, DA is widely distributed in brain regions closely associated with learning and memory processes, including, the prefrontal cortex, hippocampus and striatum. The activity of the working memory is in the prefrontal cortex. Previous study revealed that the depletion of DA produces an impairment of working memory (Surmeier, 2007).

It has been reported that the intra-hippocampal application of D2 receptor agonists improves the performance of spatial working memory, while the antagonist blockade of these receptors hinders its efficient performance (Wilkerson and Levin, 1999). The intracortical application of D1 receptor antagonists produces an impaired performance of spatial working memory (Sawaguchi and Goldman-Rakic, 1991) in rats (Seamans et al., 1995).

Regarding RISP, the present results showed that RISP attenuate the action of PPA in increase spontaneous alternation and percent of correct alt. The present results agreed with Torres-Lista et al. (2019). Despite dopamine D2 receptor blockade impairs spatial learning and memory (Beninger, 2006) in most novel antipsychotic drugs, RISP has a highest ratio of serotonin 5-HT2 receptor binding to D2 binding (Hertel, 2006). In addition, risperidone has moderately high affinity for D2 receptors and a very low affinity for dopamine D1 receptors (Bymaster et al., 1996). The dose of risperidone used in the current study was relatively low. Counterbalance the D2 stimulation, thereby reducing the occurrence of spatial orientation impairments and could attenuating stereotyped behaviors with similar result in mouse model for autism (Silverman et al., 2010).

The present results indicated that nettle leaves have a poor effect on the animal performance in Y maze task when compared to the PPA which may be due to it is neither working on monoamine neurotransmitter system nor bioenergetics system that end up with no change in the result of spontaneous alternation and percent of correct alternation. On other hand, nettle root increased the number of alternations and number of correct alternations in Y maze when compared to PPA treated groups. Because NR elevated the level of monoamines neurotransmitter (5-HT, NE, DA) in the prefrontal cortex and midbrain which have a high impact on spatial memory and learning and attenuate stereotype behavior produced by PPA. There is an evidence that in the recovery of
information related to conditioned responses in a passive avoidance paradigm in rats, the activity of DA is involved in mechanisms of information processing that determine the behavioral strategy, while 5-HT activity is more closely related with the emotional mechanisms that underlie memory (Molodtsova, 2006). The levels of DA and 5-HT in the prefrontal cortex and midbrain are involved in cognitive functions associated with behavioral reinforcement and are activated concomitantly with activation of both dopaminergic and serotonergic activity. It has been demonstrated that DA differentially affects the ‘working’ component of short-term memory and that in the striatum both DA and 5-HT are released only in relation to the working memory component (Karakuyu et al., 2007). There is evidence that DA release is mediated by serotonergic activity both in the prefrontal cortex where it is stronger as well as in the striatum. The present results are in consistent with the results of Patel and Udayabanu (2014) who indicated that nettle extract attenuates the memory dysfunction.

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