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Gongronema latifolium Modulates *Rauwolfia vomitoria*-Induced Behaviour and Histomorphology of the Cerebral Cortex

Gongronema latifolium Modula los Cambios de Comportamiento e Histomorfología de la Corteza Cerebral Inducidos por *Rauwolfia vomitoria*

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SUMMARY: *Rauwolfia vomitoria* (RV) has potent sedative effect, which may result in severe unpleasant consequences if not controlled. This necessitated this study on the effect of *Gongronema latifolium* (GL) on RV-induced behaviour, biochemical activities, and histomorphology of the cerebral cortex. Eighteen male Wistar rats of average weight 266 g were grouped into three (1–3). Group 1 was the control administered 0.5 mL of Tween®20, while groups 2 and 3 were administered 150 mg/kg of RV, and a combination of 150 mg/kg of RV and 200 mg/kg of GL (RV+GL), respectively for seven days. Twelve hours after treatments, open field neurobehavioral test was carried-out and the animals euthanized. Their sera were analyzed, and their cerebral cortices routinely processed by H&E method. There was lower ($p<0.05$) ambulatory, rearing and freezing activities in the RV group, while there was no difference in aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase activities, as well as serum cholesterol and triglycerides levels in all the groups. Cerebral cortical neurohistology of RV and RV+GL groups showed most neurons appearing hypertrophied with pyknotic nuclei in some, and less cellular population compared with the control group. RV produces sedative behaviour, and cerebral cortical neurohistological changes, which GL combination may help modulate.

KEY WORDS: *Rauwolfia vomitoria*; *Gongronema latifolium*; Behavior; Enzymes; Lipid; Cerebral cortex; Histomorphology.

INTRODUCTION

Rauwolfia vomitoria is a plant of the family *Apocynaceae* used traditionally in the treatment of snakebites, fever, nervous disorders, cerebral cramps, jaundice and gastrointestinal disorders (Kutalek & Prinz, 2007). The major phytochemical constituents of this plant include the alkaloids, glycosides, polyphenols, and reducing sugars (Akpanabiatu, 2006). The alkaloids rauwolfine, reserpine, rescinnamine, serpentine, ajmaline serpentinine, steroid-serposterol and saponin are some of the active *R. vomitoria* constituents (Gill, 1992).

R. vomitoria is reported to be useful in lowering blood pressure (Amole, 2003), and has antimalarial, antipyretic, analgesic and haematinic properties (Amole *et al*., 1993; Amole & Onabanjo, 1999; Amole *et al*., 2006; Amole & Ogunjere, 2001). There are reports that *R. vomitoria* increases haemoglobin, red blood cell and platelet counts, and has potential anticonvulsant and antipsychotic properties (Amole *et al*., 2009; Bisong *et al*., 2013). Sedative effects and decreased anxiety are amongst the neurological effects of this plant (Eluwa *et al*., 2009; Bisong *et al*., 2010). Other reports showed that the plant decreases brain glutamate activity, and increases serum albumin, gamma-aminobutyric acid, glutamic acid decarboxylase, alanine aminotransferase and alkaline phosphatase activities (Akpanabiatu *et al*., 2009; Eteng *et al*., 2009; Ebuehi & Aleshinloye, 2010).

Researches on *R. vomitoria* has shown a range of useful neural effects (Amole *et al*., 2009; Ebuehi & Aleshinloye; Bisong *et al*., 2010, 2013). Adverse effects

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include psychotic depression, poor coordination, dizziness, hallucination, and distortions of the cerebella cells and layers among others (Eluwa *et al*.). Sedation by *R. vomitoria* though useful may become adverse if the effect is not controlled. Co-administration of *R. vomitoria* with other herbal plant may help modulate this effect. This need lead to this study on the co-administration of *R. vomitoria* with *Gongronema latifolium.*

G. latifolium belongs to the family Asclepiadaceae, and is a plant primarily used as spice and vegetable (Ugochukwu & Babady, 2002; Ugochukwu *et al*., 2003). It contains essential oils, saponins and pregnanes among others (Schneider *et al*., 1993; Morebise *et al*., 2002). This plant has hypoglycemic, hypolipidemic, anti-inflammatory, antioxidant, antimicrobial, analgesic, anti-malarial, anti-diabetic and anti-ulcer properties (Ogundipe *et al*., 2003; Ugochukwu & Babady, 2003; Ugochukwu *et al*.; Akuodor *et al*., 2010; Nwinyi *et al*., 2008; Atawodi, 2005; Edet *et al*., 2009).

G. latifolium extracts has been reported to increase the activities of superoxide dismutase, glutathione reductase, glutathione peroxidase and glucose-6-phosphate dehydrogenase, and decreases lipid peroxidation and reactive oxygen species (ROS) concentrations (Ugochukwu & Babady, 2002; Ugochukwu & Cobourne, 2003). These properties of *G. latifolium* may make it an important herb that can interact with *R. vomitoria* to modulate/ameliorate some of its effects.

G. latifolium is reported to have high antioxidant properties (Ugochukwu & Babady, 2002; Ugochukwu & Cobourne), which is necessary against free radicals effects. It also ameliorates the effect of *R. vomitoria* on the cerebral cortex in mice (Ekong *et al*., 2014). This poses the question; can it ameliorate a *R. vomitoria*-induced cerebral cortical change in rats? Thus, this study investigated the effect of *G. latifolium* on *R. vomitoria* - induced sedative behaviour, some biochemical activities, and the neurohistology of the cerebral cortex of rats.

MATERIAL AND METHOD

Preparation of the herbs. Fresh leaves of *G. latifolium* and root bark of *R. vomitoria* were respectively, obtained from local farms in Ikono and Esit Eket, Local Government Areas of Akwa Ibom State, Nigeria, after identification by a botanist from the University of Uyo, Nigeria. These plant parts were washed-off dirt and air-dried for one week. They were ground to powder, and were extracted using 75-95 % ethanol in a Soxhlet extractor. The extracts were concentrated using a rotary evaporator and the concentrates dried in a Plus 11 Gallenkamp oven at 45–50ºC. The dry extracts obtained were stored in a refrigerator at 4ºC until used.

Determination of dosage. The herbal extracts were re-constituted using Tween® 20 (Sigma-Aldrich, Inc., P1379) as the vehicle. The equivalents of 150 mg/kg of *R. vomitoria* root-bark, and 200 mg/kg of ethanol leaf extract of *G. latifolium* were determined.

Experimental protocol. Eighteen adult male Wistar rats were obtain from the Animal House of the Faculty of Basic Medical Sciences, University of Uyo, Nigeria. They were housed in plastic cages of wire gauze roof and wood-shaves beddings, and the animals weights obtained as 220–320 g. The animals were maintained under room temperature of 25–27ºC, and 12:12 hours light and dark cycle. The animals were cared for according to the guidelines on the use of laboratory animals of the National Institute of Health (NIH) of the United States of America.

The eighteen rats were divided into three groups (1–3) of six rats each. Group 1 animals were the control administered 0.5 mL of Tween® 20. Group 2 animals was administered 150 mg/kg of ethanol root bark extract of *R. vomitoria*, while group 3 animals was administered a combination of 150 mg/kg of ethanol root-bark extract of *R. vomitoria* and 200 mg/kg of ethanol leaf extract of *G. latifolium*. The administration was in the mornings (7 AM), by oral gavages, and lasted for seven days (Table I).

Behavioural study. On day 8 (7 AM), (twenty-four hours after the last administration), the fasting animals were exposed to the open field neurobehavioural test and the animals were immediately sacrificed. The apparatus for the open field test was constructed of white plywood of 72x72 cm with 36 cm walls. One of the walls was clear Plexiglas, so the animals could be visible, and the floor was lined with clear Plexiglas. Blue lines were drawn on the floor with a marker and this were visible through the clear Plexiglas floor. These lines divided the floor into sixteen 18x18 cm squares. A central square of 18x18 cm was drawn in the middle of the open field.

Each rat was placed in the proximal extreme left square of the maze and allowed to explore the apparatus for five minutes. Motor activity (ambulatory activity) was expressed as; a total number of squares crossed (with all four feet on one square); horizontal activity (grooming); and the vertical activity (total number of rearing). Central square frequencies and duration, stretch-attend, defecation and urination were also measured.

Termination of experiment. Immediately after the behavioural test, the animals were sacrificed by chloroform anesthesia. Their thoraco-abdominal walls excised and blood aspirated from the left ventricle for the determination of serum levels of cholesterol and triglycerides, as well as the activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP).

The brain of each rat was dissected, preserved in 10% buffered formalin for seven days, and the cerebral cortex excised. The tissue sections were routinely process by Haematoxylin and Eosin method. After viewing under the light microscope, photomicrographs were obtained using a computer-operated digital microscope camera. Cellular population of each section of the cerebral cortex was quantified using ImageJ™ software.

Statistical analysis. The data obtained per group was analyzed by one-way analysis of variance (ANOVA), and the post-hoc Students Newman-Keul test determined the significance between the groups. Data were presented as mean ± standard error of mean, and $p<0.05$ was regarded as significant.

RESULTS

At the end of the experiment, there was loss in the body weight of the animals in all the groups. Group B animals treated with 150 mg/kg of *R. vomitoria* (RV) alone had a higher body weight loss ($p<0.001$) compared with the control and group C animals treated with a combination of 150 mg/kg of *R. vomitoria* and 200 mg/kg of *G. latifolium* (RV+GL). The body weight loss of the RV+GL group was however, not different from the control group. The percentage body weight loss were 17.45% for the RV group, and 10.46% for the RV+GL group compared with the control group of 8.99% (Table II).

There was lower ($p<0.05$) line crossing (ambulatory) and rearing activities in the RV group compared with the control and the RV+GL groups, but no difference was recorded in central square entry, central square duration, grooming, stretch-attend, duration, defection and urination except in freezing activity which was higher ($p<0.05$) compared with the control group. There was also no difference in these behavioural parameters in the RV+GL treatment groups compared with the control group (Table III).

There was no difference in the serum cholesterol and triglycerides levels in the treatment groups compared with the control group. Aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase activities were also not different between the treatment and the control groups (Table IV).

The histological section of the cerebral cortex of the control group showed six cortical layers, from the superficial to deep; marginal layer, cortical plate, subcortical plate, intermediate plate, subventricular, and the ventricular zones. Present in these layers were varying population of prominent neurons and glia. The marginal layer had sparsely populated glia and small-sized neurons. The cortical plate showed a dense population of neurons and glia. The subcortical plate had a less dense population of neurons and glia, while the intermediate plate, subventricular, and the ventricular zones though indistinguishable showed less dense cellular population. No obvious histopathology was observed (Fig. 1).

Table I. Schedule of treatments for the control and the test groups

Groups (n=6)	Treatment	Administration period (days)
1	Control (Tween 20)	7
2	(150 mg/kg of *RV*)	7
3	(150 mg/kg of *RV* + 200 mg/kg of	7

RV= *Rauwolfia vomitoria*; GL= *Gongronema latifolium*. Tween 20 was vehicle for the extracts.

Table II. Daily average body weight and body weight change.

Groups (n=6)	Initial body weight (g)	Final body weight (g)	Loss in weight (g)	Loss in weight (%)
1 Control (Tween 20)	225.80±2.41	205.50±2.10	20.3±0.31	8.99
2 (150 mg/kg of *RV*)	320.87±4.13	267.88±6.84	55.99±2.71*	17.45
3 (150 mg/kg of *RV* + 200 mg/kg of *GL*)	251.48±4.32	225.18±8.09	26.303.77^{NS}	10.46

RV= *R. vomitoria*; GL= *G. latifolium*. Data are presented as Mean±standard error of mean. ***= Significantly different from group 1 at $p<0.001$; c= Significantly different from group 3 at $p<0.001$; NS= Not significantly different from group 1 at $p<0.05$.

Table III. Behavioral activities in the open field maze.

Groups	Line Crossing	Central Square Entry	Central Square duration	Rearing	Grooming	Stretch-attend	Freezing duration	Defecation
	P=0.02 F=5.66	P=0.16 F=2.06	P=0.36 F=1.10	P=0.03 F=4.50	P=0.97 F=0.03	P=0.54 F=0.65	P=0.03 F=4.52	P=0.12 F=2.47
1 (Control)	27.67±4.51	0.33±0.21	0.01±0.01	16.17±3.82	4.50±1.18	0.17±0.17	1.12±0.33	3.00±0.73
2 (150 mg/kg of *RV*)	10.80±2.31*$_{,c}$	0.00±0.00^{NS}	0.00±0.00^{NS}	5.00±0.55*^{c}	4.40±2.11^{NS}	0.00±0.00^{NS}	3.03±0.64*	0.80±0.20^{NS}
3 (150 mg/kg of *RV* +200 mg/kg of *GL*)	35.60±7.53^{NS}	0.60±0.24^{NS}	0.01±0.00^{NS}	14.20±2.18^{NS}	4.00±1.34^{NS}	0.40±0.40^{NS}	1.59±0.42^{NS}	2.60±1.03^{NS}

Data are presented as Mean±standard error of mean. *= Significantly different from group 1 at p<0.05; c= Significantly different from group 3 at p<0.05; NS= Not significantly different from group 1 at p<0.05; RV= *R. vomitoria*; GL= *G. latifolium*; P= Probability level; F= F-ratio.

Table IV. Serum enzyme activities and lipid profile.

Group (n=6)	AST (nkat/L) P=0.52 F=0.69	ALT (nkat/L) P=0.61 F=0.50	ALP (nkat/L) P=0.90 F=0.10	CHO (mg/dl) P=0.35 F=1.13	TG (mg/dl) P=0.38 F=1.03
1 (Control)	1927.30±204.92	648.40±33.17	4277.66±436.03	92.30±6.55	87.00±13.97
2 (150 mg/kg of *RV*)	1554.68±307.79^{NS}	847.34±237.12^{NS}	4639.19±852.97^{NS}	79.72±5.92 ^{NS}	85.87±9.14^{NS}
3 (150 mg/kg of *RV* +200 mg/kg of *GL*)	1833.19±164.20^{NS}	837.02±132.00^{NS}	4498.83±223.43 ^{NS}	88.58±5.73 ^{NS}	105.47±8.57^{NS}

Data are presented as Mean±standard error of mean. NS= Not significantly different from group 1 at p<0.05. RV= *R. vomitoria*; GL= *G. latifolium*; AST= Aspartate aminotransferase; ALT= Alanine aminotransferase; ALP= Alkaline phosphatase; CHO= Cholesterol; TG= Triglyceride; P= Probability level; F= F-ratio.

The histological section of the cerebral cortex of Group 2 animals treated with RV showed most neurons appearing hypertrophied with some of them having pyknotic nuclei. There was less cellular population in the marginal layer, and a higher concentration of neurons in the cortical plate. The entire cellular population appeared less dense compared with the control group (Fig. 2). The histological section of the cerebral cortex of group 3 animals treated with RV+GL showed hypertrophied neurons with some pyknotic nuclei. There was less cellular population in the marginal layer, and a higher concentration of neurons in the cortical plate. The entire cellular population appeared less dense compared with the control group (Fig. 3).

The stereological estimation showed that cellular population of the cerebral cortex was lower ($p<0.01$) in the RV and RV+GL groups compared with the control group. However, the cerebral cortical cellular population of the RV group was lower ($p<0.01$) compared with the RV+GL group (Fig. 4).

DISCUSSION

This study was to investigate the effect of *G. latifolium* (GL) on *R. vomitoria*-induced sedative behavior, some biomolecules, as well as the neurohistology of the cerebral cortex of rats. Observations showed a reduction in the body weight of all the groups. The reduction in the body weight in all the groups may be due to the stress of handling in the course of the experiment (Research animal resources. University of Minnesota); this is because stress due to handling of animals affects their body weight change (Voisinet *et al*., 1997). The RV group showed lower ($p<0.001$) body weight compared with the control and the RV+GL group, an indication that the herbal extract alone may be useful in body weight gain control, but may also result in an uncontrolled body weight loss. However, the body weight loss of the RV+GL group was not different compared with the control group, which indicates that GL may have interacted with RV to modulate its effect on body weight, thus making the combination a better option for body weight control.

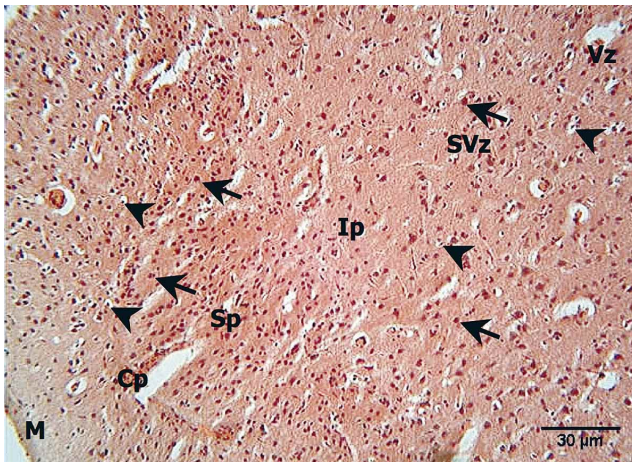

Fig. 1. Photomicrograph of the section of the cerebral cortex of the control group showed six cortical layers; marginal layer (M), cortical plate (Cp), subcortical plate (Sp), intermediate plate (Ip), subventricular (SVz), and the ventricular zones (Vz). Present in these layers were varying population of prominent neurons (long arrow) and glia (short arrow). The marginal layer had sparsely populated small-sized cells. The cortical plate (CP), showed a dense population of neurons (long arrow) and glia (short arrow). The subcortical plate showed a smaller population of neurons and glia, while the intermediate plat, subventricular, and the ventricular zones though indistinguishable had less cellular population. No obvious histopathology was observed. H &E, x160.

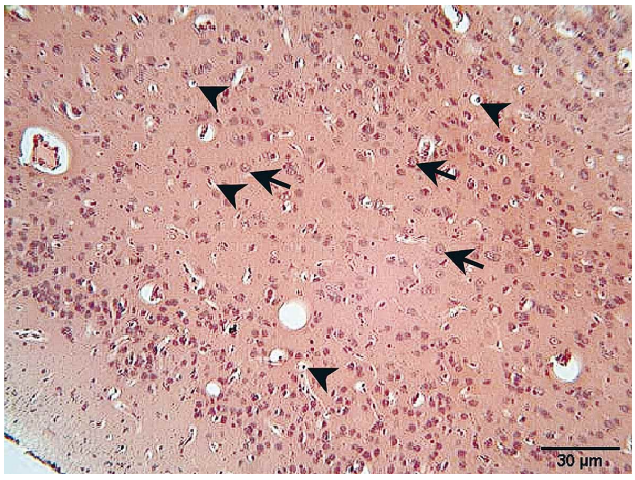

Fig. 3. Photomicrograph of the section of the cerebral cortex of group 3 animals treated with a combination of 150 mg/kg body weight of *R. vomitoria* and 200 mg/kg body weight of G. latifolium showed hypertrophied neurons with some pyknotic nuclei (long arrows) and numerous glia (small arrows). There was less cellular population in the marginal layer, and a higher concentration of neurons in the cortical plate. The entire cellular population appeared less dense compared with the control group. H&E, x160.

Body weight is an important index in the determination of the well-being of an individual, but may not be applicable

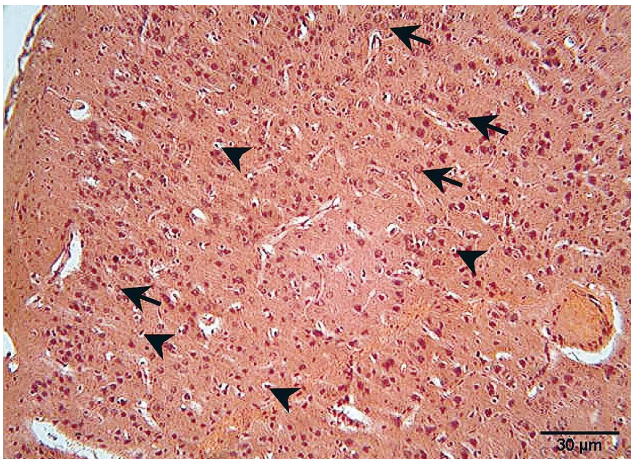

Fig. 2. Photomicrograph of the section of the cerebral cortex of Group 2 animals treated with 150 mg/kg body weight of *R. vomitoria* showed most neurons (long arrows) appearing hypertrophied with some of them having pyknotic nuclei. There was less cellular population in the marginal layer, and a higher concentration of neurons in the cortical plate. Numerous glia (small arrows) were observed throughout the entire section. The entire cellular population appeared less dense compared with the control group. H &E, x160.

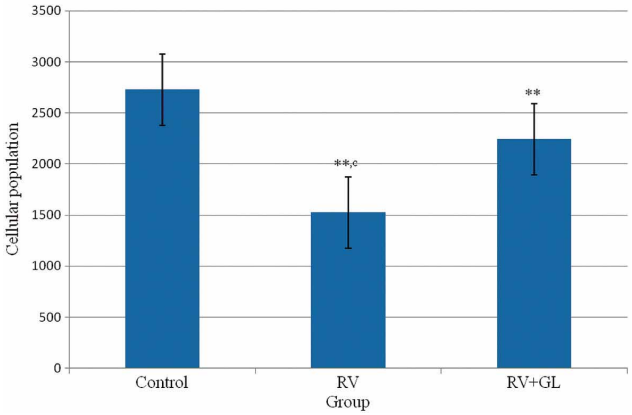

Fig. 4. Cellular population estimation

in rodents. However, body size and weight are important co-variables for describing the major pharmacokinetic parameters of xenobiotics (Poggesi, 2004). The body weight loss in this study is in line with previous studies where lower body weight of rats were reported on treatment with the extracts of R. vomitora (Eluwa *et al.*,; Ekong *et al.*, 2013; Ekong *et al.*, 2014). The present study is however, at variance with another report where mice treated with either RV alone or in combination with GL had higher body weights (Ekong *et al.*, 2014). This result may be due to the difference in animal species. It is reported that animals differ from one another in isoform composition, expression and catalytic activities of drug-metabolising enzymes (Martignoni *et al.*, 2006), which may be the case in the present study.

The open field test showed lower ($p<0.05$) ambulatory and rearing activities in the RV treatment group compared with the control and the RV+GL groups. The open field test provides a unique novel environment to assess ambulatory activities, exploration and provides an initial screen for anxiety-related behavior in rodents (Prut & Belzung, 2003). High ambulatory activity may indicate anxiogenic effect while a low ambulatory activity may indicate anxiolytic effect. The lower ambulatory and rearing activities in the RV group may also indicate sedative effect of RV on the behavioural activities of the animals.

The alkaloid, reserpine a constituent of RV has been found to have some depressive effects on the nervous system (López-Muñoz *et al*., 2004), an indication that this may be a reason for the decreased ambulatory and rearing activities in the present study. The present study is in line with previous reports (Eluwa *et al*.; Bisong *et al*., 2010, 2013). The researchers reported lower ambulatory and rearing activities with *R. vomitoria* treatments. The sedentary behavior of the animals as observed in freezing activity was higher in the RV group compared with the control, and this supports the lower ambulatory and rearing activities already reported. There was no difference in the exploratory and anxiety-like activities, which is in line with previous reports (Bisong *et al*., 2010, 2013). Eluwa *et al*., however reported a decrease in these activities, while Ekong *et al*., (2014) reported no difference in all the open field parameters. Their reports are at variance with the present study, probably due to the dosage of treatment or the animal species used.

The results also showed that there was no difference in the activities of aspartate aminotransferase, alanine aminotransferase and alkaline phos-phatase, as well as serum cholesterol and triglycerides levels in the treatment groups compared with the control group. Aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase are normally found in a variety of tissues including liver, heart, muscle, kidney and brain, and are released into the serum when any one of these tissues is damaged resulting in high serum levels (Axiomvetlab, http://www.axiomvetlab.com). The result may indicate the non-effect of the herbal extracts on these tissues. Previous reports have showed that 524 mg/kg, 2000 mg/kg and 4000 mg/kg of *R. vomitoria* increased aspartate aminotransferase, alanine aminotrans-ferase and alkaline phos-phatase activities (Eteng *et al*.; Ebuehi & Aleshinloye). Hence, the dosage of the herbs may not have been sufficient to cause the release of these enzymes.

The histological section of the cerebral cortex showed hypertrophied neurons with some showing pyknotic nuclei, and less ($p<0.01$) cellular population in the RV and RV+GL treatment groups compared with the control group. However, the cerebral cortical cellular population of the RV+GL group was higher ($p<0.01$) compared with the RV group. Hypertrophy and pyknosis are signs of cellular degeneration (Garman, 2011), and may arise when a chemical agent traumatizes the brain. Gliosis also result from trauma to the brain (Tambuyzer *et al*., 2009), and this may be a reason for the higher cellular population in the present study. Since the reported effects on the RV group were still present in the RV+GL group's cerebral cortex, it may be that the degenerative effect due to RV may not be completely reverse by GL at the dosage used in the present study. The higher cerebral cortical cellular population in the RV+GL groups compared with the RV group may also be due to neurogenesis, as some studies have shown that neurogenesis take place in the adult cerebral cortex (Jiang *et al*., 2001; Vessal & Darian-Smith, 2010).

Reports have shown that different substances and herbal extracts can protect the cerebral cortex against damage either by neurogenesis or through other mechanisms. MK-801, a non-competitive N-methyl-d-aspartate receptors antagonist, significantly alleviates neurocyte apoptosis rate and histopathological damage against methyl mercury-induced neurotoxicity (Xu *et al*., 2012). Different herbs with antioxidant properties like *G. latifolium* protect the brain against damage. *Rosmarinus officinalis* for example, protects against neuronal damage to the frontal cortex due to CCl4-induced hepatic damage (Soria Fregozo *et al*., 2012), while *Ginkgo biloba* protects against neuronal damage from free radical effect (Siddique *et al*., 2000; Loh *et al*., 2006). In addition, *G. latifolium* protects against *R. vomitoria*-induced neurotoxicity in mice (Ekong *et al*., 2013, 2014), which might also be beneficial to rats.

In conclusion, the extract of *R. vomitoria* causes sedative behaviour observed in low ambulation and rearing, and higher freezing activities, which may be ameliorated in combination *G. latifolium* treatment. In addition, the decreased cerebral cortical cellular population by the RV treatment was modulated in the combination treatment with GL.

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RESUMEN: *Rauwolfia vomitoria* (RV) tiene un efecto sedante potente, el que puede provocar graves consecuencias si no es controlado. Se estudió el efecto de *Gongronema latifolium (GL)* sobre el comportamiento inducido por RV, como también en las actividades bioquímicas, e histomorfología de la corteza cerebral.

Dieciocho ratas macho Wistar con un peso promedio de 266 g, fueron separadas en tres Grupos (1–3). El Grupo 1 (control) recibió 0,5 mL de Tween® 20, mientras que a los Grupos 2 y 3 se les administró, durante siete días, 150 mg/kg de RV y una combinación de 150 mg/kg de RV y 200 mg/kg de GL (RV + GL), respectivamente. Doce horas después de los tratamientos y pruebas neuroconductuales de campo abierto, los animales fueron sacrificados. Se analizaron los sueros y cortezas cerebrales, los cuales fueron procesados y teñidos on HE. Se observó menor actividad ambulatoria y de congelación ($p<0,05$) en el grupo RV, mientras que no hubo diferencia en la actividad aspartato aminotransferasa sérica y de fosfatasa alcalina, así como tampoco en los niveles de colesterol y triglicéridos séricos en todos los grupos. La neurohistología cortical cerebral de los grupos RV y RV + GL mostró que la mayoría de las neuronas aparecen hipertrofiadas con núcleos picnóticos, y una menor cantidad celular en comparación con el grupo control. La RV produce un comportamiento sedante, y cambios neurohistológicos a nivel de la corteza cerebral lo que podría ser modulado al combinarse con GL.

PALABRAS CLAVE: *Rauwolfia vomitoria*; *Gongronema latifolium*; Comportamiento; Enzimas; Lípidos; Corteza cerebral; Histomorfología.

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