Trop J Nat Prod Res, October 2021; 5(10):1863-1867 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Effects of Methanol Leaf Extracts of Selected Plants on the Plasma Electrolytes Levels in Preeclamptic-Induced Wistar Rats

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ARTICLE INFO

Article history:
Received 18 July 2021
Revised 15 September 2021
Accepted 03 October 2021
Published online 02 November 2021

ABSTRACT

Plants have always been used in medicine. Global research on plant medicinal efficacies has led to the development of plant-based medicines. Although their efficacy in the treatment of preeclampsia have not been shown. The study investigated the effects of methanol leaf extracts of *Jatropha curcas*, *Alchornea cordifolia* and *Secamone afzelii* on the plasma electrolytes levels of preeclampticWistar rats. The rats were given Adriamycin (3.5 mg/kg) via a lateral caudal vein after mild ether anesthesia. Female rats were coupled with reproductive male rats for 4 days after 2 weeks. In the vaginal smear, the presence of spermatozoa in the first day of pregnancy was documented. After preeclampsia was observed, the rats were administered extracts (50, 100, and 200 mg/kg body weight) orally on a daily basis during the third trimester and postpartum period. Na, K, and Cl^- plasma levels were estimated using an Automatic Electrolyte Analyzer, model BT-500 Plus; whereas Ca and Mg were analyzed by colorimetric method using standard kits. Results showed that in induced preeclampsia, sodium levels were 129.3 mmol/L in the third trimester; however, this level considerably increased to 136.3 – 170.5 mmol/L after administration of various dosages of the extracts. Calcium and magnesium levels were likewise increased (7.1 to 11.9 mg/dL and 1.05 to 2.53 mEq/L, respectively) in induced Wistar rats after extracts administration. The capacity for plant extracts to correct hyponatremia, hypocalcemia and hypomagnesemia during preeclampsia has thus been presented.

***Keywords*:** Preeclampsia, Wistar rats, Methanol leaf extracts, Electrolytes, Pregnancy, Hypertension.

Introduction

Natural medicine has sparked research interest and has led to the development of new ways for gathering and analyzing the necessary plants.[1] Plants and plant extracts are known to be effective in the management of disease conditions, and many of these plants contain chemical compounds that have been used as medicines, necessitating additional investigation. Traditional medicine practitioners utilize various portions of the plants in the treatment of a variety of illnesses, including cancer, rheumatism, hypertension, and inflammatory diseases, among others.[2]

Preeclampsia is the most common medical condition of pregnancies.[2-4] Pregnancy-induced hypertension (PIH) or toxemia is one of the main causes of maternal and perinatal mortality across the world.[3] Preeclampsia has been linked to 790 maternal fatalities per 100,000 live births.[4,5] After 20 weeks of pregnancy, preeclampsia develops, which is characterized by hypertension (high blood pressure) and proteinuria. It affects roughly 5-8 percent of all pregnancies.[6]

There are reports of complicated relationship of the concentration of electrolytes in normotensive and preeclamptic women.[7,8] Some of the reports have conflicting results.

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Citation: Atoe K and Idu M. Effects of Methanol Leaf Extracts of Selected Plants on the Plasma Electrolytes Levels in PreeclampticInducedwistar Rats.Trop J Nat Prod Res. 2021; 5(10):1863-1867. doi.org/10.26538/tjnpr/v5i10.26

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Electrolytes such as sodium and potassium play a crucial role in the smooth muscle function of the arterial walls and may play a role in the aetiopathogenesis of hypertension, as confirmed by the use of dietary sodium limitation as one of the primary treatments for high blood pressure.

Hypertension is caused by a combination of internal and the external environmental factors. The major extracellular cation, sodium, has long been thought to be a key environmental component in the pathophysiology of the disease;[9] Iwamoto and Kita[10] demonstrated that a high salt intake has a negative influence on arterial pressure. The major intracellular cation, potassium, on the other hand, has traditionally been considered a minor player in the etiology of hypertension. Potassium deficiency, on the other hand, appears to play a key role in hypertension and its cardiovascular consequences.[3,11] In normotensive subjects, a low-potassium diet (10 to 16 mmol per day) combined with their normal sodium intake (120 to 200 mmol per day) tends to result in sodium retention and an increased blood pressure; on the average, systolic increased by 6 mmHg and diastolic is increased by 4 mm Hg, and systolic pressure increased by 7 mm Hg and diastolic is increased by 6 mm.[7] Increased potassium ingestion in hypertensive rats fed high sodium diets have been found to reduce blood pressure, thereby lowering the risk of stroke and stroke-related deaths, and preventing cardiac hypertrophy, mesenteric vascular damage, and renal injury.[3,10,11] The present study was conducted to assess the effects of methanol leaf extracts of selected plants on the plasma electrolytes levels of preeclamptic Wistar rats.

Materials and Methods

Collection and preparation of plant samples

The leaves of the plants were collected in January, 2019, from First Generation Farms, Iguosula, Uhunmwonde Local Government Area,

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Edo State, Nigeria. They were identified at the Phytomedicine Unit of the Department of Plant Biology and Biotechnology, University of Benin, Benin City; authenticated and issued voucher specimen numbers by the Herbarium Unit of the same Department. The specimen numbers UBH-J404, UBH-A560 and UBHS566 were issued for *Jatropha curcas*, *Alchornea cordifolia* and *Secamone afzelii*, respectively. The plant samples were washed several times with distilled water, and then air-dried for two weeks, and then subsequently ground into powder using a Panasonic® medium kitchen blender, model MX-GX1021WTZ. Some 100 g of each powder sample was exhaustively extracted by maceration in 200 mL of methanol for 12 h; the extracts were filtered using Whatman Filter Paper No 42 (125 mm).

Study design
Wistar rats weighing 220 to 256 g were used for the investigation. The animals were kept in the Animal House in the Department of Biochemistry, University of Benin, Benin City. The animals were allowed free access to normal rodent feed (20 g protein, 0.35 g NaCl, and 1.17 g arginine per 100 g feed) and tap water *ad libitum*. They were allowed a period of 2 weeks of acclimatization before the experiment commenced.

Induction of preeclampsia
The Adriamycin Model adopted by Podjarny *et al*.[12] was used to induce preeclampsia. Under mild ether anesthesia, rats were given Adriamycin (Adriablastina, Abic) at a dose of 3.5 mg/kg i.v. into the femoral vein. The rats were coupled with a fertile male for four days. The presence of spermatozoa in the vaginal smear on the first day of pregnancy was documented. Preeclampsia was confirmed by elevated blood pressure and significant proteinuria (Table 1). Determination of blood pressure of the Wistar rat was by the non-invasive methods described by Feng and DiPetrillo,[13] using the CODA® High Throughput System with 2 Activated Channels (CODA-HT2) by Kent Scientific Corporation, USA. The rats were gently held in the restrainer of the CODA System, and the back hatch was replaced to keep the rat within. After placing all of the Wistar rats to be tested on the same CODA system in their restrainers, the rats were given 5 minutes to adapt to the restrainer before beginning the blood pressure measurement protocol. This time helps the Wistar rats to relax and warm up, allowing blood to flow to the tail. The blood pressure measuring process was initiated after a 5-minute acclimatization time.

Determination of proteinuria
Determination of proteinuria was carried out using the dipstick (combi2) method.[14]

Confirmation of preeclampsia
Increase in blood pressurefrom 124/98 mmHg to 177/121 mmHg as well as significant proteinuria confirmed preeclampsia in the induced Wistar rats (Table 1).

Table 1: Confirmation of preeclampsia

Treatments	Parameter	Control	Induced
Blood pressure			
Third trimester	Systolic (mmHg)	124	177
	Diastolic (mmHg)	98	121
Post-partum	Systolic (mmHg)	121	160
	Diastolic (mmHg)	96	125
Proteinuria			
Third trimester	Proteinuria	Negative	+++
Post-partum	Proteinuria	Negative	+

Twenty-four (24) hours after administration of the last dose of the standard drug (100 mg/kg methyl DOPA) and the extracts to the respective groups, the animals were anaesthetized with chloroform.[15]

Experimental animals
The animals were maintained in accordance with international guidelines for the care and use of laboratory animals. The Wistar rats were randomly separated into fifteen (15) groups consisting of ten (10) rats each. Group 1 served as the positive control, Groups 2, 3, and 4 served as the negative controls. Groups 5 – 15 were the preeclamptic groups. Group 5 animals did not receive any treatment. Group 6 animals were administered with the standard drug 100 mg/kg methyl DOPA (Aldomet®), Groups 7 – 15 were administered with 50, 100, 200 mg/kg of the respective plant extracts. Extracts as well as standard drugs were administered to the rats as soon as preeclampsia was achieved. This was done orally at the respective doses, once a day, until the rats were delivered of their pops.

Ethical issues
Ethical approval was obtained from the Research and Ethics committee of Faculty of Life Sciences, University of Benin, Benin City, with reference LS19017, dated March 7, 2019.

Processing blood for plasma
Blood sample was collected by cardiac puncture into heparinized bottles. The sample was then centrifuged at 3000 rpm for 5 minutes to obtain clear slightly yellow supernatant plasma.

Determination of electrolytes levels
Sodium, potassium and chloride estimation
These were estimated using an Automatic Electrolyte Analyzer, model BT-500 Plus. The mechanism of this instrument is based on the use of an ion selective electrode with a selective membrane that only enables the desired ion to pass through.[16]

Estimation of calcium and magnesium
These were estimated using the colorimetric method using standard kits from Randox and Teco Diagnostics respectively. For calcium the principle for estimation was based on the *O*-cresolphthalein complexone method, where calcium ions form a violet complex with O-crestolphthelein complex one in an alkaline medium. The intensity of the colour is directly proportional to the concentration of calcium in the plasma.[17]
For the determination of magnesium, the principle was based on magnesium forming a coloured complex with calmagite in alkaline medium to produce a red complex that is measured spectrophometrically at 530 nm. EGTA serves as a complex and prevents calcium interference and a surfactant eliminates the effects of protein. The colour produced is proportional to the magnesium concentration.[18, 19]

Statistical analysis
Data were analyzed using SPSS version 20 software, and means were separated using least significant differences at 95% probability.

Results and Discussion

Preeclampsia is pregnancy-induced hypertension and is linked to a high risk of morbidity and death, particularly during childbirth.[20] Preeclampsia patients have been known to have hypertension, as well as significant proteinuria, despite the fact that they were previously normotensive. The study evaluated the effect of some plant extracts (*Jatropha curcas*, *Alchornea cordifolia* and *Secamone afzelii*) on the plasma electrolytes levels among preeclampsia and normotensive Wistar rats.
Reduction in Na, K, Cl^-, and Mg was observed in preeclamptic rats (Table 2). Whereas Na level was 139.2 mmol/L; administration of the plant extracts to non-preeclamptic animals elevated the sodium levels to 153.3 – 158.7 mmol/L. However, incidence of preeclampsia significantly reduced sodium levels to 129.3 mmol/L. Upon administration of plant extracts, enhanced sodium levels resulted (136.3 – 170.5 mmol/L).
The hypothalamus, adrenal gland, and kidneys are the major regulators of sodium levels, which are important for regulating extracellular fluid volume and osmotic activity.[21]

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Table 2a: Electrolyte levels of preeclamptic treated and control Wistar rats at 3rd trimester

Treatments	3rd trimester				
	Na (mmol/L)	K (mmol/L)	Cl(mmol/L)	Ca(mg/dl)	Mg (mEq/L)
Control	139.2	3.7	103.1	9.0	2.01
Only Ext-A (No induced PreEc)	156.6	10.5	133.4	10.0	2.06
Only Ext-B (No induced PreEc)	153.3	6.0	114.1	9.9	1.99
Only Ext-C (No induced PreEc)	158.7	4.6	122.5	10.5	2.07
Induced PreEc, no treatment	129.3	4.7	91.2	7.1	1.05
Induced PreEc + 100 mg/kg StdD	139.3	5.6	108.4	10.5	2.06
Induced PreEc + 50 mg/kg Ext-JC	148.8	5.3	115.5	11.2	2.11
Induced PreEc + 100 mg/kg Ext-JC	136.3	3.3	101.2	11.6	2.11
Induced PreEc + 200 mg/kg Ext-JC	143.2	5.4	110.1	11.9	2.53
Induced PreEc + 50 mg/kg Ext-AC	137.6	4.0	114.5	11.4	2.16
Induced PreEc + 100 mg/kg Ext-AC	160.8	4.4	141.3	10.9	2.15
Induced PreEc + 200 mg/kg Ext-AC	170.5	5.0	136.4	11.2	2.17
Induced PreEc + 50 mg/kg Ext-SA	169.0	5.3	156.7	10.9	2.16
Induced PreEc + 100 mg/kg Ext-SA	139.9	3.0	113.2	10.8	2.22
Induced PreEc + 200 mg/kg Ext-SA	141.4	3.1	117.9	10.6	2.00
F-test	7.051	12.112	6.365	2.928	1.351
LSD(0.05)	31.3	2.9	12.1	3.0	1.1
p-value	<0.01	<0.01	<0.01	0.007	0.243

Table 2b: Electrolyte levels of preeclamptic treated and control Wistar rats at postpartum

Treatments	Post-partum				
	Na (mmol/L)	K (mmol/L)	Cl(mmol/L)	Ca(mg/dl)	Mg (mEq/L)
Control	149.6	5.4	110.4	10.6	2.3
Only Ext-A (No induced PreEc)	142.8	4.1	125.4	10.1	2.0
Only Ext-B (No induced PreEc)	135.7	5.6	113.7	10.0	2.0
Only Ext-C (No induced PreEc)	142.9	4.8	125.5	10.9	2.2
Induced PreEc, no treatment	126.3	5.0	98.7	9.7	2.0
Induced PreEc + 100 mg/kg StdD	140.0	5.0	120.2	9.9	2.0
Induced PreEc + 50 mg/kg Ext-JC	134.8	4.7	121.2	10.4	2.3
Induced PreEc + 100 mg/kg Ext-JC	141.7	5.6	122.8	10.4	2.5
Induced PreEc + 200 mg/kg Ext-JC	132.2	3.8	106.1	9.6	1.7
Induced PreEc + 50 mg/kg Ext-AC	139.8	5.2	110.3	9.5	2.1
Induced PreEc + 100 mg/kg Ext-AC	170.4	5.6	136.4	10.9	2.3
Induced PreEc + 200 mg/kg Ext-AC	131.3	3.3	113.3	8.7	1.7
Induced PreEc + 50 mg/kg Ext-SA	159.8	5.3	133.2	9.8	2.0
Induced PreEc + 100 mg/kg Ext-SA	142.2	4.5	103.0	8.6	1.7
Induced PreEc + 200 mg/kg Ext-SA	147.6	5.6	126.9	10.7	2.4
F-test	1.284	1.753	1.298	1.679	1.648
LSD(0.05)	13.7	2.7	15.2	3.6	1.1
p-value	0.273	0.096	0.265	0.114	0.123

Ext-JC, Methol leaf extract of *Jatropha curcas;* Ext-AC, Methol leaf extract of *Alchornea cordifolia;* Ext-SA, Methol leaf extract of *Secamone afzelii.*StdD - Standard drug was Methyl DOPA (Aldomet®); Ca = Calcium, K = Potassium, Na = Sodium, Cl = Chlorine, Mg = Magnesium

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

When compared to normotensive Wistar rats, plasma sodium and potassium levels were much lower and the findings were consistent with a previous study by Darkwa et al.[22, 23] Furthermore, the result in this study disagrees with the study of Gordon[24] who reported women with preeclampsia; plasma sodium was above the normal reference range, whereas it was within the normal reference interval in normotensive pregnant and normotensive non-pregnant women. Electrolyte levels in preeclampsia patients do not alter.[25] The effects of sodium on blood pressure are caused by two processes. Excess sodium consumption causes intracellular and extracellular plasma volume expansion, resulting in increased blood flow and cardiac output, which causes peripheral vascular resistance. Increased endothelium damage causes sodium and water retention, which causes angiotensin production. The baroreceptors produce an antidiuretic hormone (ADH) in response to a reduction in plasma volume, leading to water retention. A low sodium level, which is seen in preeclampsia, results from the secretion of antidiuretic hormones improperly by the placenta.[21]

Aldosterone is a mineralocorticoid that causes sodium to drag water along during salt reabsorption from the kidney, resulting in an increase in blood pressure and, as a result, an increase in blood pressure. Patients with hypertension are believed to have greater aldosterone and sodium levels, however in this study we found that in preeclampsia, there was low sodium levels rather than high sodium levels, the reduction may be due to syndrome of inappropriate ADH expression. ADH is believed to have been released by the posterior pituitary gland in the brain. ADH acts by attaching to specific receptors on the kidney, interacting with the vasopressin (V2) receptor, triggering the mobilization of aqua-porins water channels from the basolateral to the apical surface of the distal convulated tubules and collecting duct thereby promoting water reabsorption. In preeclamptic patients, the placenta produces ADH which increases water reabsorption into the blood, leading to a dilutionalhyponatremia. Upon administering the various plant extracts, it was observed that the extract had the potential to correct the low sodium levels.

The extracts also caused a significant increase in plasma chloride levels from 91.2 mmol/L to 101.2 – 156.7 mmol/L in preeclamptic rats treated with 50 mg/kg *Secamone afzelii* leaf extract, with the highest levels recorded from preeclamptic rats treated with 50 mg/kg *Secamone afzelii* leaf extract. Despite the fact that preeclamptic rats had reduced Ca and Mg levels in the blood plasma; these electrolyte levels were restored after plant extracts were administered. When preeclamptic rats were administered 100 mg/kg methanol leaf extract of *Alchornea cordifolia* throughout the postpartum period, the best findings were observed. Abubakar and Sule[25] found similar results. Abnormal sodium and/or potassium concentrations in the blood can influence the osmotic pressure of the body fluid, which is linked to blood pressure. The connection between sodium and hypertension is based on sodium's ability to "attract" water. When the plasma sodium level rises, the body retains water, lowering the sodium concentration and causing hyperkalaemia and hyponatremia. This might cause the osmotic pressure of the body fluid to change. This is because irregular sodium and/or potassium concentrations in the blood can influence the osmotic pressure of the body fluid, which is linked to blood pressure. The results in Table 3 showed that there was strong significant correlation (r = 0.961** and 0.873**, p<0.001) between Mg and Ca during the 3rd trimester and post-partum, respectively. However, a weak correlation with Na (r = 0.40 and 0.38) was observed.

The significant decrease in potassium (K) levels found in the induced preeclamptic group is consistent with Anjum and Alka's[26] findings. Increased plasma levels of aldosterone and other mineralocorticoids may cause hypokalemic alterations in normal pregnancy.[10] Potassium deficiency in the body is caused by insufficient potassium conservation by the kidneys and alimentary canal; fecal potassium losses might surpass urine losses.[26] Khan et al.,[27] on the other hand reported no significant change in these electrolyte levels in preeclamptic women.

There have been fewer investigations on the role of chloride (Cl^-) in the pathophysiology of preeclampsia. There was a significant increase in plasma Cl^- levels in the induced preeclamptic rats. Increased plasma Cl^- levels may cause an increase in osmolality, resulting in reduced vascular dilatation.[28]

Calcium and magnesium levels were found to be significantly low. This is similar to the study carried out by Darkwa *et al.*[22, 23] and Narayana et al.[29] Hypomagnesemia is one of the causes of hypocalcemia. Low magnesium levels can lead to low calcium levels. Hypomagnesemia is closely linked to hypocalcemia, which is caused by a decrease in parathyroid hormone (PTH) secretion or a resistance of PTH in bone and renal tubules.

Table 3: Bivariate correlation among sodium, calcium and magnesium levels during preeclampsia

Correlations		3rd trimester			post-partum		
		Na	**Ca**	**Mg**	**Na**	**Ca**	**Mg**
Na	Pearson Correlation	1.00	0.36	0.40	1.00	0.49	0.38
	Sig. (2-tailed)		0.271	0.225		0.125	0.251
Ca	Pearson Correlation	0.36	1.00	***0.961*** **	0.49	1.00	***0.873*** **
	Sig. (2-tailed)	0.271		<0.001	0.125		<0.001
Mg	Pearson Correlation	0.40	***0.961*** **	1.00	0.38	***0.873*** **	1.00
	Sig. (2-tailed)	0.225	<0.001		0.251	<0.001	

Na = Sodium, Ca = Calcium, Mg = Magnesium

Conclusion

Based on the present findings, it can be inferred that increasing blood pressure causes a significant decrease in plasma sodium, potassium, calcium, and magnesium levels in preeclamptic Wistar rats. The administration of methanol leaf extracts of *Jatropha curcas*, *Alchornea cordifolia* and *Secamone afzelii* corrected the abnormalities.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgements

The Authors gratefully acknowledged Mr Francis Aibuedefe Igiebor of Wellspring University, Benin City, for typesetting the manuscript. The contributions of Dr. Beckley Ikhajiagbe of the Department of Plant Biology and Biotechnology, University of Benin, Nigeria, is highly acknowledged.

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