Cardiology and Angiology: An International Journal

9(3): 31-37, 2020; Article no.CA.58003
ISSN: 2347-520X, NLM ID: 101658392

Protective Effects of *Thymus schimperi* and *Moringa stenopetala* Leaf Extracts on Arterial Blood Pressure and Urine Protein Level in Pre-eclampsia Rat Models

Kumlachew Mergiaw[1*], Yoseph A. Mengesha[2], Tesfaye Tolessa[2], Eyasu Makonnen[3], Solomon Genet[4], Abiy Abebe[5], Kidist Gebreyesus[6], Ashenif Tadele[5], Asfaw Debella[5] and Demeke Ashencho[7]

[1]Department of Physiology, Debre Berhan University, Ethiopia.
[2]Department of Physiology, Addis Ababa University, Ethiopia.
[3]Department of Pharmacology, Addis Ababa University, Ethiopia.
[4]Department of Biochemistry, Addis Ababa University, Ethiopia.
[5]Ethiopian Public Health Institute, Addis Ababa, Ethiopia.
[6]Department of Horticulture, Debre Berhan University, Ethiopia.
[7]St. Paul's Millennium Medical College, Addis Ababa, Ethiopia.

Authors' contributions

This work was carried out in collaboration among all authors. Author KM designed the study, performed the experimental procedures, statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors YAM, TT, EM and SG wrote the 2nd draft of the manuscript and supervised lab experiments. Author AA assisted in calibrating BP recording machine and sample collections. Authors KG, AT, AD and DA organized data, managed the literature searches, assisted plant material preparation. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/CA/2020/v9i330137
Editor(s):
(1) Gen-Min Lin, Hualien-Armed Forces General Hospital, Taiwan.
Reviewers:
(1) Nihad Abdul-Lateef Ali Kadhim, AL -Qasim Green University, Iraq.
(2) Mohamed Fayed Abdel-Hameed, National Research Centre, Egypt.
(3) Oluwakemi Funmilola Ashubu, University College Hospital Ibadan, Nigeria.
Complete Peer review History: http://www.sdiarticle4.com/review-history/58003

Original Research Article

Received 12 April 2020
Accepted 17 June 2020
Published 27 June 2020

ABSTRACT

Background: Pre-eclampsia (PE) is a common hypertensive disorder during pregnancy and one of the leading causes of perinatal mortality and morbidity. There is no curative modern drug to treat PE. Therefore, researches done on traditional medications have paramount importance in

**Corresponding author: E-mail: kumlachew23@gmail.com;*

discovering therapeutic and /or protective agents from plant materials. In Ethiopia, there are claims that some indigenous medicinal plants such as *Thymus* and *Moringa* can have potential protective functions against PE. The aim of this study was to prove the claims.

Methods: Experiments were performed to investigate the effects of aqueous leaf extracts of *Thymus schimperi* (ALETS) and *Moringa stenopetala* (ALEMS) on PE rat models induced by nitro-L-arginine methyl ester (L-NAME); a nitric oxide synthase inhibitor. A non-invasive tail cuff blood pressure recorder (Model 179 Amplifier, IITC INC, Life Science Instruments, Woodland Hills, California) was used to determine the arterial blood pressure from rat tail. Urine analysis to determine protein levels was performed using a dipstick, semi-qualitative method as per manufacturer's instructions (CYBO DFI Korea).

Results: ALETS treated PE rat models showed significantly reduced mean arterial blood pressure (MAP) in mmHg; 108±3 ($P<0.05$), 105±1 ($P<0.01$) and 99±2 ($P<0.01$); also the same pattern of results were seen in ALEMS treated PE groups with MAP of 106±1 ($P<0.05$), 103±1 ($P<0.05$) and 101±1 ($P<0.05$) at daily doses of 250 mg/kg, 500 mg/kg and 1000 mg/kg, respectively, compared to untreated case group that had 123±3.7 mmHg at gestation day (GD) 19 . Untreated PE rat models showed significant proteinuria (2000±20 mg/L) throughout the gestation period; while PE rat models treated with either ALETS or ALEMS had significantly reduced ($p<0.05$) proteinuria in dose dependent pattern (150±15 mg/L) at a dose of 1 gm/kg for each plant extract at GD 19.

Conclusion: Aqueous leaf extracts of either *Thymus schimperi* or *Moringa stenopetala* might reduce and control arterial pressure in PE rat models in a dose dependent manner. The extracts also could reduce level of proteinuria in the same pattern. Further investigation should, however, be carried out to confirm their uses in prevention and/or treatment of pregnancy-induced hypertension among human cases.

Keywords: Blood pressure; pre-eclampsia; proteinuria; protective; extract; Thymus schimperi; Moringa stenopetala; rat models.

ABBREVIATIONS

ALEMS- aqueous leaf extracts of Moringa stenopetala, ALETS- aqueous leaf extracts of Thymus schimperi ANOVA-analysis of the variance, BP-blood pressure, CHS-college of health sciences, DBP- diastolic blood pressure, EPHI- Ethiopian Public Health Institute, GD-gestation day, HELLP-hemolysis, elevated liver enzymes and low platelets, L-NAME- nitro-L-arginine methyl ester, MAP- mean arterial blood pressure, PE- pre-eclampsia, PIH-Pregnancy induced hypertension, SBP- systolic blood pressure, S.E.M-standard error of the mean.

1. INTRODUCTION

Pregnancy induced hypertension (PIH) represents a group of health threats associated with elevated blood pressure during pregnancy, proteinuria and sometimes coma and convulsions. Serious complications on the mother and her baby might result from pre-eclampsia (PE) and eclampsia which are the main clinical types of PIH [1,2]. These disorders are associated with vasospasm, pathologic vascular lesions, increased platelet activation and subsequent activation of the coagulation system in the micro-vasculature [3], metabolic changes, endothelial dysfunction, and increased inflammatory response [4]. Eclampsia is usually the consequence of pre- eclampsia consisting of central nervous system seizures which often make the patient unconscious leading to death [5]. PE occurs in 2 to 8% of pregnant women and classically manifests as new-onset hypertension and proteinuria after 20 weeks of gestation. The National High Blood Pressure Education Program Working Group defined 'Pre-eclampsia/ eclampsia' is a blood pressure ≥140/90mmHg in association with proteinuria ≥ 300 mg in 24 hrs urine diagnosed after 20^{th} week of gestation [6,7]. Human pregnancy usually gets complicated with pregnancy induced hypertension (PIH) in considerable magnitude with no curative modern medicines [8]. PE occurs in 2 to 8% of pregnant women and classically manifests as new-onset hypertension and proteinuria after 20 weeks of gestation [9]. Recent discoveries, have led to important advances in understanding the pathogenesis of the condition. Placental anti-angiogenic factors are up regulated and disrupt the maternal endothelium [10]. This change in the normal angiogenic balance toward an anti-angiogenic state can result in hypertension, proteinuria, glomerular endotheliosis, HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome and cerebral edema as

clinical signs of PE and eclampsia [11-13]. Treatment of pre-eclempsia associated hypertension with modern drugs is difficult. The only known cure for PE is delivery of the placenta. Use of nitric oxide inhibitors are, therefore, one of the best methods of inducing animal model of PE which might help to test various therapeutic or preventive strategies [14]. On the other hand, there are traditional claims that plants can effectively treat this condition. For instance, in many countries of Africa, many people with high blood pressure eat leaves of *Moringa* and Thymus plants to get relief from their ailment. Few studies tried to prove such traditional claims, and reported that these plants could significantly drop arterial blood pressure. In Ethiopia, *Thymus schimperi* which grows in an open grassland, edges of roads, on bare rocks and on slopes, in the altitude range of 2200-4000 meters above sea level [15,16], has antihypertensive and diuretic activities in animal studies [17]. Moreover, *Thymus serrulatus* (another endemic species) is reported to have vasodilatory activities [18] the other plant *Moringa stenopetala,* which is the dominant species is cultivated in terraced fields in Ethiopia;has blood pressure lowering effects [19]. All these might support the traditional claims that both plants could have anti- hypertensive activities thus, both plants may help in the treatment of pregnancy induced hypertension. The objective of this study was, therefore to invesigate the potential protective effects of the aforementioned plants against PE.

2. METHODS

2.1 Blood Pressure Recording

Blood pressure was measured by non-invasive tail cuff method using blood pressure analyzer (Model 179 Amplifiers; IITC INC. /Life Science Instruments; Woodland Hills, California). Each pregnant rat was placed in individual restraining cage. Then, arterial blood pressure recording was conducted continuously for 2-hours period after stabilization for 1 hour. At least 5 serial recordings which had similar values were recorded and the average was considered as the final value. Arterial pressure was determined every other day before gestation day 10 then every day from day 11 to day 19 of gestation in all groups of rats. The analyzer had tracings for the systolic blood pressure (SBP) and mean blood pressures (MAP). Diastolic blood pressure (DBP) recording was calculated using the common physiologic method to estimate MAP; MAP=DBP +1/3 * (SBP-DBP).

2.2 Experimental Animal Models

Virgin and well matured female Wistar Albino rats (weight of 200-250 grams and age, 3-6 months) were purchased from Ethiopian Public Health Institute (EPHI). The animals were housed at room temperature between 20°C and 25°C with relative humidity of 30% to 70%. Dark and light cycle each of 12 hours was followed. The animals were acclimatized to laboratory condition for one week before commencement of experiment and dosing. Observational examination by animal health workers was done prior to and at the end of the acclimatization period. All animals were in free access to water and food (standard commercial pellet). The animals were identified by cage number, animal number and individual marking on fur (tail). All the experimental procedures and protocols used in current study were reviewed and approved by the Institutional Review Board (IRB) of College of Health Sciences of Addis Ababa University. Those female rats which were in estrous phase (identified by microscopic demonstration of typical epithelial cells on vaginal smear) were housed and co-habited with fertile male rats of the same species in a ratio of 2:1. (F: M) over night. The gestation day one (GD1) was depicted as the day that copulation occurred as demonstrated by the presence of vaginal plug and sperm cells on vaginal plug hence pregnancy, the male rats were separated from the female rats. The animals were randomly grouped in to groups (n=6) as follows: G-I (normal control) G-II (untreated PE rat models, G-III (nifedipine (20 mg/kg/d orally) treated PE rat models (reference treated)G-IV rat models treated with ALETS include three dosing subgroups (G-IV-1 oral dose of 250 mg/kg/d, G-IV-2 oral dose of 500 mg/kg/d G-IV-3 oral dose of 1000 mg/kg/d) G-V rat models treated with ALEMS include three dosing subgroups (G-V-1 oral dose of 250 mg/kg/d, G-V-2 oral dose of 500 mg/kg/d G-V-3 oral dose of 1000 mg/kg/d).

N (ω)-nitro-L-arginine methyl ester (L-NAME), widely used inhibitor of nitric oxide synthase (NOS) activity both *in vitro* and *in vivo*), was used to induce PE in rats with oral doses of 50mg/kg/d starting from GD11 using the method by [20,21]. Nifedipine (calcium channel blocker) was used as a standard anti-hypertensive agent in reference treated control group (G-III) with a

dose of 20 mg/kg/d. To obtain urine sample, each rat was kept in a metabolic rat-cage and the 24 hrs urine sample was collected. The urine protein level was determined using a dipstick, semi-qualitative method as per manufacturer's instructions (CYBO DFI Korea) at GD10 (used as baseline), GD13 (to confirm PE-induced proteinuria) and then after, (to evaluate the effects of the extracts or drug) which is preferred method to confirm proteinuria [22].

2.3 Plant Material Preparation

One kilogram of leaves of each plant (*Thymus* and *Moringa*) material was collected. Then the plant samples were identified by a plant taxonomist and voucher numbers (01/2016Tc and 02/2016Ms) were given and deposited at the National Herbarium of Addis Ababa University. The fresh leaves were cleaned and dried under shade at room temperature. Then, dried leaves were reduced by manual crusher to obtain powder. The powdered leaves from each plant were macerated with cold distilled water for 4 hours with intermittent agitation by an orbital shaker. Then, the supernatant part of agitated materials were decanted and filtered with Whatman's filter paper number 4. The filtrates were freeze-dried at -20°C and reduced pressure, and then lyophilized to obtain aqueous crude extracts. The extracts were kept in a desiccator at room temperature until experimental use.

2.4 Data Processing and Analyses

All experimental data were expressed as mean values ± standard error of the mean (S.E.M) and were subjected to bio-statistical interpretation by SPSS windows version 21 statistical packages all the way using a one-way ANOVA followed by post-hoc test (Tukey Test) for multiple comparisons of the mean differences and responses to extracts and drugs. Statistical significance of $P < 0.05$ was considered as level of significance.

3. RESULTS

3.1 Comparative Protective Effects of ALETS and ALEMS on BP of PE Rat Models

Comparative protective effects of different doses of ALETS and ALEMS on BP records were determined in PE rat models and compared with untreated control group. Hence, PE rat models that were treated by either of the aforementioned extracts had significantly ($p<0.05$) controlled and stabilized SBP and DBP with in normal range in a dose dependent manner compared to untreated PE cases (G-II). ALETS treated PE rat

Table 1. Comparative protective effects of ALETS on arterial blood pressure in PE rat models

BP (mmHg)	Groups						
	GD	G-I	G-II	G-III	G-IV rat models treated with ALETS		
					G-IV-1 (250 mg/kg)	G-IV-2 (500 mg/kg)	G-IV-3 (1000 mg/kg)
SBP	10	119±4	113±2	113±3	107±3	117±3	118±2
	12	118±6	169±8^{a***e**}	114±3^{b***}	145±5^{a**b*c**e*}	144±3^{a**b*c**e*}	143±5^{a**b*c**e*}
	16	117±6	161±6^{a**}	105±8^{b***e*}	134±1^{a*c**}	126±1^{a*c**}	116±1^{a*c**}
	19	104±6	166±4^{a***}	93±10^{b***e*}	130±4^{a**b*c**}	125±4^{a**b*c**}	113±4^{a**b*c**}
DBP	10	81±4	79±1	77±2	76±1	83±4	83±2
	12	75±3	114±13^{a*e*}	80±9^{b*}	101±1^{e*}	99±4^{e*}	95±1^{e*}
	16	75±3	101±13^{a**}	81±8^{b**}	103±1^{a*}	96±3^{a}	92±1^{a*}
	19	71±2	106±2^{a***}	63±7^{b***e*}	97±3^{a**c***}	95±1^{b**c***}	92±2^{a*c**}
MAP	10	94±3	90±2	88±2	86±3	94±2	94±2
	12	89±3	132±11^{a***e*}	92±7^{b***}	115±1^{e*}	114±4^{e*}	111±1^{e*}
	16	89±3	121±10^{a*}	89±8^{b*}	113±1^{a*c*}	106±3	100±1
	19	82±3	123±4^{a***}	73±8^{b***e*}	108±3^{a**c***}	105±1^{a**b*c***}	99±2^{a**b*c***}

Mean ±SEM $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$, ^{a}p-compared to normal controls (G-I), ^{b}p-compared to untreated controls (G-II); ^{c}p-compared to reference treated (G-III), ^{d}p-compared to extract received counterparts, ^{e}p-progressive change across serial gestation days (GD), G-I (normal control) G-II (untreated PE rat models of PE) G-III (nifedipine (20 mg/kg/d orally) treated PE rat models (reference treated),G-IV rat models treated with ALETS include three dosing subgroups (G-IV-1 oral dose of 250 mg/kg/d, G-IV-2 oral dose of 500 mg/kg/d G-IV-3 oral dose of 1000 mg/kg/d), SBP-systolic blood pressure, DBP-diastolic blood pressure, MAP-mean arterial pressure, n=6

Table 2. Comparative protective effects of ALEMS on arterial blood pressure in PE rat models

BP (mmHg)	Group						
	GD	G-I	G-II	G-III	G-V rat models treated with ALEMS		
					G-V-1 (250 mg/kg)	G-V-2 (500 mg/kg)	G-V-3 (1000 mg/kg)
SBP	10	119±4	113±2	113±3	115±2	116±2	113±2
	12	118±6	169±8$^{a***\ e*}$	114±3^{b***}	152±3$^{a**c***\ e*}$	145±2$^{a**c***\ e*}$	142±3$^{a**c***\ e*}$
	16	117±6	161±6^{a**}	105±8^{b***}	142±9	138±1^{b*c**}	135±1^{b*c**}
	19	104±5	166±4^{a***}	93±10^{b***}	138±5^{a**b*c***}	137.±3^{a**b*c***}	134±2^{a*b**c**}
DBP	10	81±4	79±1	77±2	79±2	76±2	76±2
	12	75±3	114±13$^{a*\ e*}$	80±9^{b*}	100±1 ^{e*}	99±1 ^{e*}	98±2 ^{e*}
	16	75±3	101±13^{a**}	81±8^{b**}	91±4^{b*}	88±1^{b*}	81±1^{b**}
	19	71±2	106±2^{a***}	63±7^{b***}	90±1^{a*c**}	87±1^{a*c***}	85±1^{b**c**}
MAP	10	94±3	90±2	88±2	91±1	89±3	88±1
	12	89±3	132±11$^{a***\ e*}$	92±7^{b**}	117±2$^{a*\ e*}$	114±2 ^{e*}	112±1 ^{e*}
	16	89±3	121±10^{a*}	89±8^{b*}	108±9	104±1	99±2^{b*}
	19	82±3	123±4^{a***}	73±8^{b***}	106±1^{a**b*c***}	103±1^{a*b**c**}	101±1^{a*b**c**}

*Mean ±SEM *P<0.05; **P<0.01; ***P<0.001, [a]p-compared to normal controls (G-I), [b]p-compared to untreated controls (G-II); [c]p-compared to reference treated (G-III), [d]p-compared to extract received counterparts, [e]p-progressive change across serial gestation days (GD), G-I (normal control) G-II (untreated PE rat models of PE) G-III (nifedipine (20 mg/kg/d orally) treated PE rat models (reference treated),G-V rat models treated with ALEMS include three dosing subgroups (G-V-1 oral dose of 250 mg/kg/d, G-V-2 oral dose of 500mg/kg/d G-V-3 oral dose of 1000 mg/kg/d), SBP-systolic blood pressure, DBP-diastolic blood pressure, MAP-mean arterial pressure, n=6*

models (G-IV-1, G-IV-2 & G-IV-3) showed, well reduced and controlled SBP (130±4, 125±4 &113±4), DBP (97±3, 95±1 & 92±2) and MAP (108±3, 105±1 &99±2) compared to ALEMS treated counterparts (G-V-1, G-V-2 & G-V-3) that had SBP 138±5, 137.±3 &134±2 in the 3 dose levels, DBP (90±1, 87±1 & 85±1), MAP (106±1, 103±1 & 101±1) with daily doses of 250 mg/kg, 500 mg/kg and 1000 mg/kg respectively at GD19 (Tables 1 and 2).

3.2 Comparative Protective Effects of ALETS and ALEMS on Urine Protein Level of PE Rat Models

Based on this study, L-NAME induced PE groups had significant proteinuria which were similar with human cases. PE rat models that received either of the extracts showed significantly ($p<0.05$) reduced urine level of protein in a dose dependent manner compared to untreated controls (G-II) (Table 3).

Table 3. Urine levels of protein (mg/L) among different groups of rats at different gestational days

Groups	Level of Proteinuria (mg/L) across gestation days (GD)			
	GD 1O	GD 12	GD 16	GD 19
G-I	150±3	150±5^{b*}	150±5^{b*}	15±3^{b*}
G-II	150±3	2000±42^{a**e*}	2000±10^{a**}	2000±20^{a**}
G-III	150±2	2020±9$^{a**\ e*}$	900±10^{a*b**}	15±2$^{b***\ e*}$
G-IV-1	150±5	2100±6$^{a**\ e*}$	1780±10^{a**}	1500±20^{a**}
G-IV-2	150±6	2020±5$^{a**\ e*}$	1650±20^{a**}	1500±15^{a**}
G-IV-3	150±5	2000±3$^{a**\ e*}$	1420±10^{a*}	150±15$^{b**\ e*}$
G-V-1	150±5	2050±5$^{a**\ e*}$	1800±10^{a**}	1500±10^{a**}
G-V-2	150±5	2200±5$^{a**\ e*}$	1300±10^{a**}	1500±15^{a**}
G-V-3	150±5	2150±5$^{a**\ e*}$	1150±20^{a*}	150±15$^{b**\ e*}$

*Mean ±SEM *P<0.05; **P<0.01; ***P<0.001, [a]p-compared to normal controls (G-I), [b]p-compared to untreated controls (G-II); [c]p-compared to reference treated (G-III), [d]p-compared to extract received counterparts, [e]p-progressive change across gestation days (GD), G-I (normal control) G-II (untreated PE rat models of PE) G-III (nifedipine (20 mg/kg/d orally) treated PE rat models (reference treated), G-IV rat models treated with ALETS include three dosing subgroups (G-IV-1 oral dose of 250 mg/kg/d, G-IV-2 oral dose of 500 mg/kg/d G-IV-3 oral dose of 1000 mg/kg/d),G-V rat models treated with ALEMS include three dosing subgroups (G-V-1 oral dose of 250 mg/kg/d, G-V-2 oral dose of 500 mg/kg/d G-V-3 oral dose of 1000 mg/kg/d), n=6*

4. DISCUSSION

From the results of this study, it is indicated that, PE animal models that were treated with either of the study extracts, showed significantly controlled BP. The potential candidate phytochemicals in both plants subjected for regulating the blood pressure parameters in PE rat models might be Coumarins, Tannins and Polyphenols through their vasodilating and anti-oxidant properties. Because, generalized vasoconstriction and oxidative stress that cause endothelial injuries are full markings in the pathogenesis of PE [23,24]. Based on the current findings, no significant difference was observed in protective actions among the two extracts. The results were in line with previous reports upon anti-hypertensive effects of same extracts on chronic hypertensive models [25]. PE rat models that received either ALETS or ALEMS showed significantly reduced urinary protein level compared to untreated PE group. The result was in line with outcomes of PE treatment with standard anti-hypertensive drugs [26]. However, there are no previous studies done about the effects of these extracts on PE animal models to compare results. Therefore the present study gives insights about the potential protective effects of the plant extracts on this common reproductive disorder and could be serving as base line finding for future investigations.

5. CONCLUSION AND RECOMMENDATION

The results of this study may hint the potential protective options of the two plant extracts that have demonstrated activities on reduction and control of the abnormal blood pressure records close to the normal ranges in rats. This study has indicated promising results about the protective roles of *ALETS* and *ALEMS* against PE. However, further investigations with other models of PE need to be conducted.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Ethical approval was obtained from Institutional Review Board of College of Health Sciences of Addis Ababa University with a protocol number of 029/16/032/16/ Physio; Prior to the initiation of the experiment.

AVAILABILITY OF DATA AND MATERIAL

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Tesfaye G, Tilahun R. Pregnancy induced hypertension and associated factors among women attending delivery service at Mizan-Tepi University Teaching Hospital, Tepi General Hospital and Gebretsadik Shawo Hospital, Southwest, Ethiopia. Ethiop J Health Sci. 2019;29(1): 831–840.
2. Mammaro A, Carrara S, Cavaliere A, Cavaliere A, Ermito S, Dinatale A, Pappalardo E, Militello M, Pedata R. Hypertensive disorders of pregnancy. J Prenat Med. 2009;3(1):1-5.
3. Harsha S, Deepti S. Assessment of platelet indices in pregnancy induced hypertensive patients versus normotensive pregnant patients. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2019;8(5):1-5.
4. Powe C, Levine R, Karumanchi S. Preeclampsia, a disease of the maternal endothelium: The role of antiangiogenic factors and implications for later cardiovascular disease. Circulation. 2011; 123(24):2856-2869.
5. Marilyn J, Richard P. Seizures in women with preeclampsia: Mechanisms and management. Fetal Matern Med Rev. 2011;22(02):91–108.
6. Owiredu L, Turpin N. Putative risk factors of pregnancy-induced hypertension among Ghanaian pregnant women. Journal of

Medical and Biomedical Sciences. 2012; 1(3):62-76.
7. Coppage K, Sibai B. Preeclampsia and eclampsia. Women's Med. 2008;1(1): 1756-2228.
8. Andrea G, Vesna D. The management of hypertension in pregnancy. Adv Chronic Kidney Dis. 2013;20(3):229–239.
9. Arun J. Epidemiology of preeclampsia: Impact of obesity. Nutr Rev. 2013;71(1):1-4.
10. Gathiram P, Moodley J. Pre-eclampsia: Its pathogenesis and pathophysiology. Cardiovascular Journal of Africa. 2016; 27(2):1-5.
11. David A. Savitz J. Pregnancy-induced hypertension in North Carolina. American Journal of Public Health. 1992;82(5):675–679.
12. Joey P, Barbara T, Maria T, William A, Raouf A. Pathophysiology of hypertension during pre-eclampsia linking placental ischemia with endothelial dysfunction. Hypertension. 2001;38(1):718-722.
13. Young B, Levine R, Karumanchi S. Pathogenesis of preeclampsia. Annu Rev Pathol. 2010;5(1):173-192.
14. Chandrasekhar Y, Robert E. Inhibition of nitric oxide synthesis in rats during pregnancy produces signs similar to those of pre-eclampsia. American Journal of Obstetrics and Gynecology. 1993;165(5): 1316-1320.
15. Asfaw N, Storesund H, Skattebol L, Tonnesen F, Aasen A. Volatile oil constituents of twoThymus species from Ethiopia. Flavor and Fragrance Journal. 2000;15(1):123-125.
16. Abera T, Debebe E, Ashebir R, Abebe A, Basha H, Kasahun T. Phytochemical constituents, safety and efficacy study of *Thymus schimperi* and *Thymus serrulatus*. J Clin Exp Pharmacol. 2019; 10(1):263-267.
17. Haji H, Makonnen E, Debella A, Bekesho G. Evaluation of diuretic and anti-hypertensive activity of leaf extracts of *Thymus schimperi* in Rats. Ann Clin Lab Res. 2016;4(1):1-5.
18. Bekesho G, Mebrahtu E, Selamu K, Asfaw D, Eyasu M, Abiy A. In vitro vasodilatory effect of aqueous leaf extract of Thymus serrulatus on thoracic aorta of Guinea pigs. Asian Pac J Trop Biomed. 2015;5(1):15-19.
19. Mengistu A, Abebe Y, Mekonnen Y, Tolessa T. *In vivo* and *in vitro* hypotensive effect of aqueous extract of *Moringa stenopetala*. African Health Sciences. 2012;12(4):545-551.
20. Molnar S, Toth H. Prolonged blockade of nitric oxide synthesis in gravid rats produces sustained hypertension, proteinuria, thrombo-cytopenia, and intrauterine growth retardation. Am J Obstet Gynecol. 1994;170(5):1458-1466.
21. Podjarny E, Losonczy G, Baylis C. Animal models of preeclampsia. Semin Nephrol. 2004;24(6):596-606.
22. Chang C, Su M, Ho J. The efficacy of semi-quantitative urine protein-to-creatinine (P/C) ratio for the detection of significant proteinuria in urine specimens in health screening settings. Springer Plus. 2016;5(1):1791-1798.
23. Siddiqui A, Jaleel A, Alkadri H, Akram S, Tamimi W. Biomarkers of oxidative stress in women with pre-eclampsia. Biomark Med. 2013;7(2):229-234.
24. Mutlu T, Ademoglu I, Aykaç U. Imbalance between Lipid Peroxidation and Anti-oxidant Status in Preeclampsia. Gynecol Obstet Invest. 1998;46(1):37-40.
25. Bekesho G, Eyasu M, Asfaw D, Ashenif T. *In vivo* antihypertensive and anti-hyperlipidemic effects of the crude extracts and fractions of *Moringa stenopetala* (Baker f.) Cufod. Leaves in Rats. Frontiers in Pharmacology. 2016;7(1):97-108.
26. Catherine M, Vesna D. Drug treatment of hypertension in pregnancy. Drugs. 2014; 74(3):283–296.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/58003