International Journal of Medical and Health Research
ISSN: 2454-9142
www.medicalsciencejournal.com
Volume 4; Issue 9; September 2018; Page No. 139-143

Novel strategies using plausible markers to predict preeclampsia

Dr. Aruna Rachel[1*], Dr. Sushil Pakyanadhan[2], Dr. Sudeep Abraham[3]
[1] Dr. VRK Womens College and Hospital, Aziz nagar, Hyderabad, R.R. District, Telangana, India
[2] Shadan Institute of Medical Sciences, Himayatsagar Road, Hyderabad, Telangana, India
[3] SIMS hospital, 6-50, Adarsh Nagar, Serilingampally, Hyderabad, Telangana, India

Abstract
Preeclampsia, hypertensive disorder of pregnancy is characterized by hypertension, proteinuria occurring following the 20th week of gestation in previously normotensive pregnant women. Though many scientific clinical and biochemical tests have been anticipated for prediction of preeclampsia there is not enough substantiation for their use in clinical practice. Emerging novel strategies like targeting the CSE/H2S activity, role of marinobufagenin in the development of hypertension, have been investigated only in animal models of preeclampsia. Further research, requiring clinical trials may provide some evidence for their use as a part of the treatment strategies. Keeping in mind, the possible drawbacks with respect to the current investigative procedures, this review highlights on how the altered level of plasma thiols i.e. elevated cysteine, homocysteine, cysteinylglycine and decreased glutathione levels and increased serum CRP levels in subjects with abnormal doppler (proneness to preeclampsia) could be used as risk marker to predict preeclampsia. This review additionally highlighted on how L-Arginine administration in subjects with abnormal doppler decreased the plasma thiols and serum CRP levels back to their existing normal range in a normotensive pregnant woman. Endothelial dysfunction could be associated with the presence of raised concentrations of CRP and plasma thiols that alters the production and degradation of Nitric oxide.

Keywords: preeclampsia, pregnancy, CRP levels

Introduction
Hypertensive disorders of pregnancy are associated with significant maternal and fetal mortality and morbidity, preeclampsia being the most common one [1]. It has been defined as "a new onset of elevated blood pressure of 140/90 mm Hg or more, recorded on two separate occasions at least 6 hours apart and in the presence of at least 0.3g of protein in a 24 hour urine, occurring after the 20th week of gestation in a previously normotensive patient, and resolving completely between 6-12 weeks after delivery" [2].
This condition is known to occur in early pregnancy because of abnormal placentation leading to impaired trophoblastic differentiation; the process further stimulating oxidative stress and resulting in a systemic inflammatory response. On the other hand, late onset preeclampsia (i.e. ≥34 weeks gestation) is triggered by an intrinsic pathology involving microvillus overcrowding impeding the perfusion resulting in increased oxidative stress proteins that modulate the maternal response to developing preeclampsia through regulation of various growth factors [3].
As per the World Health Organization (WHO) (2003), the incidence of preeclampsia is high in developing countries (2.8% of live births) than in developed countries (0.4%) [4]. It is known to complicate 3% to 8% of the pregnancies in westernized countries accounting for about 10 – 15% of the overall maternal deaths [5]. The four major etiologic factors implicated in the pathologic process are immunological maladaptive tolerance between maternal and fetal tissues, abnormal trophoblastic invasion of the uterine arteries, maternal mal adaptation to cardio vascular system and genetic factors [6].
Dysfunction of the L-Arginine-Nitric oxide system occurs in preeclampsia leading to lowered nitric oxide levels [7]. The inflammatory marker C-reactive protein is associated with endothelial dysfunction, possibly due to a reduced bioavailability of Nitric oxide (NO) [8]. Cysteine, homocysteine, cysteine glycine and glutathione are the biologically low molecular mass thiols found in the plasma(9) and according to a well known theory, excess free radicals triggers off preeclampsia in those women who have lowered level of glutathione and higher levels of cysteine, homocysteine and cysteinyl glycine [10].
With respect to diagnosis, uterine artery Doppler continues to be the main clinical adjunct, but suffers from low sensitivity. Hypothetically, added information might come from prenatal diagnostic analytics (first trimester, plasma protein-A [PAPP-A]; second trimester alpha-fetoprotein [AFP], human chorionic gonadotropin [hCG], and inhibin-A), but large prospective data analysis performed as a part of the National Institute of Child Health and Human Development Maternal Fetal Medicine Units Network antioxidant trials was disappointing [11]. This review was directed towards knowing if the plasma thiol and CRP levels would help predict this condition and to further analyze the nitric oxide levels after administering the drug L-Arginine.

Diagnostic tests for preeclampsia
Doppler velocimetry to assess the impedance of uteroplacental flow in pregnancies was first described in the 1980s (12). This method detects using abnormal wave patterns in the Doppler

ultrasound [13]. Systematic review and meta-analysis to assess the accuracy of mean arterial pressure and blood pressure measurements in predicting this disease, elucidated mean arterial pressure as a better predictor than systolic, diastolic or an increased blood pressure [14]. The spot protein: creatinine ratio to identify proteinuria of 0.3 g/day or more in hypertensive pregnancy was reviewed by Cote AM, *et al.* [15].
Angiogenic markers, mainly placental growth factor showed considerable potential in the diagnosis [16]. Congo red test assessed the presence of misfolded proteins in urine as a diagnostic and prognostic tool by combining smart phone based image analysis with molecular disease specific features [17]. L Yoffe reviewed the prognostic value of circulating small non-coding RNA in the first trimester, for use as a non-invasive diagnostic tool [18].

Thiel status in women with preeclampsia

Apart from the major etiologic factors implicated in the pathologic process, lately evidence has been established for the role of oxidative stress which can be combated by enzymatic/non enzymatic antioxidants [19]. Thiols encompass the major fraction of the whole body of antioxidants and play a key role in defense against the reactive oxygen free radicals [20]. Cysteine, homocysteine, cysteine glycine and glutathione group of thiols help in combating this oxidative stress [21].
A study on homocysteine association with preeclampsia found higher mean levels in women with preeclampsia (14.5) in comparison to normotensive pregnant women (11.5) [22]. Similar trends were found in the study conducted by Raijmakers *et al.* [19] with respect to mean homocysteine and cysteinyl glycine levels in preeclampsia and normal pregnancies. This elevated concentration in preeclamptic patients could be attributed to decreased activity of one of the enzymes responsible for the remethylation of homocysteine or pathological process of haemoconcentration [23].
Literature assessing the glutathione activity noted a very significant decrease in plasma glutathione peroxidase activity in preeclamptic pregnancies when compared to controls [24]. Reports given by JB Sharma, *et al.* [25] and S Kharb [26] found a comparable trend of reduced glutathione level in pre eclamptic women. Glutathione neutralizes the free radicals and reactive oxygen species in preeclampsia and thereby protects the macromolecules against this oxidative damage. This decrease in the glutathione levels might be due to disturbances in the synthesis of glutathione in this condition [23].
Study (my PhD thesis) done to predict preeclampsia using a doppler ultrasound also found elevated levels of cysteine, homocysteine and cysteinyl glycine and decreased levels of glutathione in those with abnormal doppler when compared to subjects with normal Doppler. These altered levels of oxidative stress parameters could be used as a plausible marker to predict preeclampsia in pregnant women.

C-reactive protein to predict preeclampsia

C-reactive protein (CRP) was recognized way back in the 1930s to be linked with one of the pathogenic process i.e. acute inflammatory responses [27]. It is formed by the hepatocytes in the liver [28]. In a normal pregnancy, improved innate immune cell activation is seen in the periphery. In distinction, preeclamptic pregnancies are associated with improper immune responses [29]. Inflammatory cytokines like interleukin-6 along with tumor necrosis factor-α are elevated in this condition [30]. These stimulate the production of C-reactive protein [31], which is an extremely objective and sensitive index of overall inflammatory activity in the body [32].
Prior literature to estimate serum uric acid and C-reactive protein levels found an elevated mean of 8.14 in preeclampsia in contrast to subjects with normal pregnancy (6.28) [33]. A case control study to determine the (CRP) level along with fibrinogen concentration demonstrated a high maternal serum CRP in preeclampsia compared with those from normal pregnant women [34]. H Ayatollahi, *et al*. [35] and AJ Onuegbu, *et al*. [36] too reported considerable difference in the means serum CRP involving normal pregnant women and preeclamptic women.
Study (my PhD thesis) using a doppler ultrasound also found high mean levels of serum CRP in abnormal doppler group (2.9) in contrast to normal doppler (2.1). CRP, a sensitive marker of tissue damage and inflammation played an important role in eliciting response characteristic of preeclampsia [37]. A relationship between endothelial dysfunction and inflammation was established [38, 39] and it was additionally revealed that markers of endothelial activation have an active role [40]. These high levels of CRP occurring as a consequence of dysfunction of endothelial cells [41] may perhaps be used as risk marker for predicting preeclampsia

L-Arginine dependent nitric oxide metabolism & its effect on thiols and CRP

Although the etiopathogenesis is still uncertain, there is a compromised function of maternal endothelium i.e. vasoconstriction with increased peripheral resistance and hypertension [42]. In subjects with preeclampsia, plasma levels of asymmetric dimethyl-arginine (ADMA), an endogenous inhibitor of Nitric Oxide (NO) synthesis, is found to be elevated [43, 44]. This decreased synthesis and bioavailability of NO has been suggested to play a role in this condition [45]. Although, exogenous application of NO showed improved fetoplacental circulation, recent reports confirmed impaired endothelial function after prolonged use of these drugs [46, 47].
In this regard, stimulation of synthesis of NO by use of a substrate for nitric oxide synthase (NOS), L-Arginine seems safer. Intriguingly, whether this promotes endothelial synthesis and reverses endothelial dysfunction and therefore improves the clinical status of the patients is still uncertain [48].
Infusion of 30 g of L-Arginine was reported to reduce blood pressure and increase plasma levels of L- citrulline and nitrite; noteworthy, these effects were greater in uncomplicated than preeclamptic pregnancies [49]. Zdebski Z, *et al*. [50] on the other hand, denied a hypotensive effect of L-Arginine given in a daily oral dose of 12 g, up to 5 days.
Importantly, in both the above mentioned studies L-Arginine was given in high amounts over short periods of time. When we take into consideration the complex nature of endothelial dysfunction one should expect a significantly longer time for its reversal. Surprisingly, only a few studies addressed the question of the effects of L-Arginine administered over a prolonged period of time. The study conducted at Osmania Medical College, Hyderabad, Dr VRK Women's Medical

College and Hospital, Hyderabad, Shadan Institute of Medical Sciences, Hyderabad was the first of its kind in which a relatively low dose was administered for longer than 1 week showed that there was a statistically significant lowered levels of serum nitric Oxide (p value of < 0.0001) in those cases who had an abnormal doppler and who eventually developed pre eclampsia and an improvement in the nitric oxide levels of those women who had a nitric oxide donor supplementation (L-Arginine) (my PhD thesis)

My study further went ahead to evaluate the plasma level of these thiols and serum CRP in patients with abnormal Doppler after the administration with L-Arginine. Findings of the study elucidated a very interesting finding, the increased level of thiols and serum CRP reverted back to the normal range of values. One possible reason could be the re-methylation process involving adenosyl intermediates (inhibitor of nitric oxide synthase) which could be competed away with L-Arginine, the natural substrate of nitric oxide synthase [51].

Novel therapeutic targets and emerging treatments

Magnesium sulphate

In a Cochrane appraisal, magnesium sulphate had halved the risk of eclampsia, and possibly reduced maternal death attributing to it [52]. It is frequently given either by intramuscular or intravenous routes. The intramuscular regimen is 4 g intravenous loading dose, followed by 10 g intramuscularly and then 5 g intramuscularly every 4 hours. The intravenous regimen is 4 g dose, followed by maintenance infusion of 1 to 2 g/h by controlled infusion pump [53].

Angiogenesis

A dysregulation of angiogenesis is elucidated in the pathogenic mechanism of preeclampsia. Placental cystathionine γ-lyse (CSE) expression is decreased, leading to reduced plasma levels of hydrogen sulfide (H2S). Targeting this CSE/H2S activity may be a possible treatment therapy [54].

Marinobufagenin

The role of marinobufagenin (MBG) in animal models of preeclampsia demonstrated an inhibited cytotrophoblast cell function and the urinary excretion of MBG was high prior to the development of hypertension and proteinuria which could be a potential target for treatment in preeclampsia [55].

Poly ADP ribose polymerase (PARP)

Contribution of PARP to endothelial dysfunction prevented the development of both endothelial dysfunctions along with hypertension, in a rat model of preeclampsia [56].

Conclusion and future perspective

Preeclampsia has remained a major public health threat in developed as well as developing countries contributing to maternal morbidity and mortality. The problem is confounded by the etiology besides the capricious nature of the disease. Results of my study showed statistically lowered levels of serum nitric oxide levels in those who had an abnormal Doppler and who eventually developed pre eclampsia and an improvement in those who had a nitric oxide donor supplementation (L-Arginine). The thiols and CRP were also analyzed and there were abnormal level in those with the disease ($p<0.001$). Additionally in my study L-Arginine administered to subjects with abnormal Doppler decreased the thiols and CRP levels back to their normal range. Endothelial dysfunction could be associated with the presence of raised concentrations of CRP and plasma thiols that altered the production and degradation of Nitric oxide. This review gives an additional scope for research where L-Arginine supplements could be used to improve endothelial function resulting from altered production of nitric oxide. Prevention of any disease progression requires the accessibility of methods for prediction of those at high risk for the disorder. Currently available investigative procedures are limited by financial constraints and local resource settings. Henceforth altered levels i.e. increased serum cysteine, homocysteine, cysteinyl glycine and serum CRP and decreased glutathione could be used as plausible markers to predict this disease.

References

1. Arun Jeyabalan. Epidemiology of preeclampsia: Impact of obesity. Nutr Rev. 2013; 71(01):1-14.
2. Baker PN. (Ed). Obstretics by Ten Teachers. 18th Edition, London, Arnold. 2006; 42(46):158-170.
3. English FA, Kenny LC, McCarthy FP. Risk factors and effective management of preeclampsia. Integrated Blood Pressure Control. 2015; 8:7-12.
4. Dolea C, AbouZahr C. Global Burden of hypertensive disorders of pregnancy in the year, 2000.
5. Evidence and information for policy World Health Organization, 2003, 1-11.
6. Uzan J, Carbonnel M, Piconne O, Asmar R, Ayoubi JM. Pre eclampsia: Pathophysiology, diagnosis, and management. Vasc Health Risk Manag. 2011; 7:467-474.
7. Gathiram P, Moodley J. Pre eclampsia: its pathogenesis and Pathophysiology. Cardiovasc J Afr. 2016; 27(2):71-78.
8. Morris NH, Eaton BM, Dekker G. Nitric oxide, the endothelium, pregnancy and pre-eclampsia. BJOG. 1996; 103:4-15.
9. CDA Stehouwer, *et al*. Systemic inflammation is linked to low arginine and high ADMA plasma levels resulting in an unfavourable NOS substrate-to-inhibitor ratio: the Hoorn Study. Clinical Science. 2011; 121:71-78.
10. Turell L, Radi R, Alvarez B. The thiol pool in human plasma. The central contribution of albumin to redox processes. Free Radic Biol Med. 2013; 65:244-253.
11. Raijmakers MT, Zusterzeel PL, Steegers EA, Hectors MP, Demacker PN, Peters WH. Plasma thiol status in preeclampsia. Obstet Gynecol. 2000; 95(2):180-4.
12. von Dadelszen P, *et al*. Improving maternal and perinatal outcomes in the hypertensive disorders of pregnancy: A vision of a community-focused approach. International Journal of Gynecology and Obstetrics. 2012; 119:S30-S34.
13. Campbell S, Diaz-Recasens J, Griffin DR, Cohen-Overbeek TE, Pearce JM, Willson K, Teague MJ. New Doppler technique for assessing uteroplacental blood flow. Lancet. 1983; 1:675-7.

14. Casmod Y, Dyk BV, Nicolaou E. Uterine artery Doppler screening as a predictor of pre - eclampsia. Health SA Gesondheid. 2016; 21:391-396.
15. Cnossen JS, Vollebregt KC, de Vrieze N, *et al*. Accuracy of mean arterial pressure and blood pressure measurements in predicting pre-eclampsia: systematic review and meta-analysis. BMJ: British Medical Journal. 2008; 336(7653):1117-1120.
16. Côté AM, Brown MA, Lam E, *et al*. Diagnostic accuracy of urinary spot protein:creatinine ratio for proteinuria in hypertensive pregnant women: systematic review. BMJ : British Medical Journal. 2008; 336(7651):1003-1006.
17. Duhig KE, Shennan AH. Recent advances in the diagnosis and management of pre-eclampsia. F1000Prime Reports. 2015; 7:24.
18. Stephan Michael Jonas, Thomas Martin Deserno, Catalin Sorin Buhimschi, Jennifer Makin, Michael Andrew Choma. Irina Alexandra Buhimschi; Smartphone-based diagnostic for preeclampsia: an mHealth solution for administering the Congo Red Dot (CRD) test in settings with limited resources. Journal of the American Medical Informatics Association. 2016; 23(1):166-173.
19. Yoffe L, *et al.* Early Detection of Preeclampsia Using Circulating Small non-coding RNA. Scientific Reports, 2018, 8.
20. Raijmakers MT, Roes EM, Zusterzeel PLM, Steegers EAP. WHM Peters. Thiol status and antioxidant capacity in women with a history of severe pre eclampsia. BJOG. 2004; 111(3):207-12.
21. Prakash M, Shetty MS, Tilak P, Anwar N. Total Thiols: Biomedical Importance and Their Alteration in Various Disorders. OJHAS, 2009, 8(2).
22. Turell L, Radi R, Alvarez B. The thiol pool in human plasma. The central contribution of albumin to redox processes. Free Radic Biol. Med. 2013; 65:244-253.
23. Urmila S, Guptha HP, Singh RK, Manju S, Seema M, Shwetha P. Homocysteine: Association with preeclampsia and Normotensive pregnancy. J Obstet Gynecol India. 2009; 59(3):235-238.
24. Modupe Fisayo ASAOLU, *et al*. Plasma thiol levels in pregnancy induced hypertension in Nigerians. Arch. Apll. Sci. Res. 2010; 2(2):443-447.
25. Mistry HD, Wilson V, Ramsay MM, Symonds ME, Pipkin FB. Reduced Selenium Concentrations and Glutathione Peroxidase Activity in Preeclamptic Pregnancies. Hypertension. 2008; 52:881-888
26. Sharma JB, Sharma A, Bahadur A, Vimala N, Satyam A, Mittal S. Oxidative stress markers and antioxidant levels in normal pregnancy and pre eclampsia. International journal of Gynecology and Obstetrics. 2006; 94(1):23-27.
27. Kharb S, Gulati N, Singh V, Singh GP. Superoxide Anion Formation and Glutathione Levels in Patients with Preeclampsia. Gynecol Obstet Invest. 2000; 49:28-30.
28. Gammil HS, *et al*. Does C - reactive protein predict recurrent preeclampsia? Hypertens Pregnancy. 2010; 29(4):399-40.
29. Mirzaie F, *et al*. Association of Maternal Serum C – Reactive Protein Levels with Severity of Preeclampsia. Acta Medica Iranica, 2009, 47(4).
30. Harmon AC, *et al*. The role of inflammation in the pathology of pre eclampsia. Clin Sci. (Lond). 2016; 130(6):409-419.
31. Lamarca B. The role of immune activation in contributing to vascular dysfunction and the pathophysiology of hypertension during preeclampsia. Minerva Ginecol. 2010; 62:105-120.
32. Parchim NF, *et al*. Neurokinin 3 receptor and phosphocholine transferase: missing factors for pathogenesis of C-reactive protein in preeclampsia. Hypertension. 2015; 65:430-439.
33. Qiu C, *et al*. A prospective study of maternal serum C-reactive protein concentrations and risk of preeclampsia American Journal of Hypertension. 2004; 17(2/1):154-160.
34. Mandal KK. Serum uric Acid and C-Reactive Protein in Preeclampsia.IOSR-JDMS. 2015; 14(2):16-23.
35. Samakoosh MA, Yazdani S, Bouzari Z, Golsorkhtabaramiri M. Maternal serum C-reactive protein and fibrinogen concentration in women with pre-eclampsia. Caspian J Reprod Med. 2015; 1(2):10-13.
36. Ayatollahi H, Hasanzade M, farzadnia M, Khabbaz Khoob M, Rahmanian A. seum level of High Sensitive C-Reactive protein in Normal and Preeclamptic Pregnancies. Iraninan Journal of Pathology. 2007; 2(3):100-104.
37. Onuegbu AJ. Evaluation of High-Sensitivity C-Reactive Protein and Serum Lipid Profile in Southeastern Nigerian Women with Pre-Eclampsia. Med Princ Pract. 2015; 24:276-279.
38. Redman CW, Sacks GP, Sargent IL. Preeclampsia: An excessive maternal inflammatory response to pregnancy. Am. J Obstet. Gynecol. 1990; 180:499-506.
39. Zimmerman GA, Prescott SM, McIntyre TM. Endothelial cell interaction with granulocytes, tethering and signaling molecules. Immunol Today. 1992; 13:93-100.
40. Mantovani A, Dejana E. Cytokines as communication signals between leukocytes and endothelial cells. Immunol Today. 1989; 10:370-375.
41. Teran E, Escudero C, Moya W, *et al*. Elevated C-reactive protein and pro-inflammatory cytokines in Andean women with pre-eclampsia. Int J Gynaecol Obstet. 2001; 75:243-249.
42. Yusuf Ustun, Yapral Engin-Ustun, Mansur Kamaci. Association of fibrinogen and Creactive preotein with severity of preeclampsia, Eur. J Obstet. Gynecol. Reprod Biol. 2005; 121:154-158.
43. Wang Y, Gu Y, Zhang Y, Lewis DF. Evidence of endothelial dysfunction in preeclampsia: decreased endothelial nitric oxide synthase expression is associated with increased cell permeability in endothelial cells from preeclampsia. Am J Obstet Gynecol. 2004; 190:817-24.
44. Facchinetti F, Longo M, Piccinini F, Neri I, Volpe AL. arginine infusion reduces blood pressure in preeclamptic women through nitric oxide release. J Soc Gynecol Invest 1999; 6: 202-207
45. Pettersson A, Hedner T, Milsom II. Increased circulating concentrations of asymmetric dimethyl arginine (ADMA), an endogenous inhibitor of nitric oxide synthesis, in preeclampsia Acta Obstet Gynecol Scand. 1998; 77:808-13.

46. Lowe DT. Nitric oxide dysfunction in the pathophysiology of preeclampsia, Nitric Oxide. 2000; 4:441-458.
47. Nakatsuka M, Takata M, Tada K, Asagiri K, Habara T, Noguchi S, *et al*. A long-term transdermal nitric oxide donor improves uteroplacental circulation in women with preeclampsia. J Ultrasound Med. 2002; 21:831-836.
48. Warnholtz A, Tsilimingas N, Wendt M, Munzel T. Mechanisms underlying nitrate-induced endothelial dysfunction: insight from experimental and clinical studies. Heart Fail Rev. 2002; 7:335-345.
49. Preli RB, Klein KP, Herrington DM. Vascular effects of dietary l-arginine supplementation. Atherosclerosis. 2002; 162:1-15.
50. Facchinetti F, Longo M, Piccinini F, Neri I, Volpe AL. arginine infusion reduces blood pressure in preeclamptic women through nitric oxide release. J Soc. Gynecol. Invest 1999; 6:202-207.
51. Zdebski Z, Gryglewski RK, Rytlewski K, Kostka-Trabka E. l-arginine in pregnancy complicated by hypertension - a preliminary report. J Drug Dev Clin Pract, 1996, 7327-7330.
52. Balligand JL. Vitamin B or L Arginine supplementation in Hyperhomocysteinaemia: think twice. Cardiovascular Research. 2012; 96:165-166.
53. Duley L, Gulmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. Cochrane database of systematic reviews, 2010, 11CD000025.
54. Lu JF, Nightingale CH. Magnesium Sulfate in Eclampsia and Pre-Eclampsia Clin Pharmacokinet. 2000; 38:305.
55. Wang K, Ahmad S, Cai M, Rennie J, Fujisawa T, Crispi F, *et al*. Dysregulation of hydrogen sulfide producing enzyme cystathionine gamma-lyase contributes to maternal hypertension and placental abnormalities in preeclampsia. Circulation. 2013; 127(25):2514-2522.
56. Uddin MN, Horvat D, DeMorrow S, Agunanne E, Puschett JB. Marinobufagenin is an upstream modulator of Gadd45a stress signaling in preeclampsia. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2011; 1812(1):49-58.
57. Walsh SK, English FA, Crocker IP, Johns EJ, Kenny LC. Contribution of PARP to endothelial dysfunction and hypertension in a rat model of pre-eclampsia. British journal of pharmacology. 2012; 166(7):2109-2116.