Gynecology & Obstetrics

Kilari et al., Gynecol Obstet (Sunnyvale) 2014, 4:1
http://dx.doi.org/10.4172/2161-0932.1000195

Review Article Open Access

A Novel Molecular Mechanistic Hypothesis to Validate the Therapeutic Effects of *Tribulus terrestris* (Gokshur) to Ameliorate Pathophysiology and Improve Pregnancy and Fetal Outcome in Preeclampsia

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Abstract

Preeclampsia is a pregnancy hypertensive disorder which leads to both maternal and fetal morbidity and mortality. Evidences suggest that factors such as maternal micronutrients and oxidative stress are involved in the pathology of preeclampsia. Studies on preeclampsia and preterm have shown altered maternal micronutrients (folic acid, vitamin B12) and their probable epigenetic mechanisms leading to metabolic and neurobehavioral disorders in the offspring in later life. Our earlier study has also shown increased oxidative stress and reduced birth outcome in preeclampsia. Reports also suggest that micronutrients deficiency is prevalent in Indian women leading to oxidative stress and adverse pregnancy outcomes. However, studies on supplementation with micronutrients/synthetic antioxidants have shown controversial results in preeclampsia. Further, there are no reports on supplementation with natural antioxidant rich Ayurved herbal agents in preeclampsia. *Tribulus terrestris* (TT) is aprostate herb, used extensively in traditional Indian medicine (Ayurved) to treat inflammatory (Shotha), cardiovascular (Hridroga) and renal disorders. TT has been advised during sixth month of pregnancy in Ayurveda to maintain pregnancy. Further, several clinical and experimental studies have validated the effects of TT in cardiovascular, hepatic and reproductive disorders due to its antioxidant and antihypertensive activities. However, no studies have examined the effect of TT in the prevention/treatment of preeclampsia and fetal programming. Hence, future studies should investigate the efficacy of TT along with micronutrients like folate and vitamin B_{12} in the treatment of preeclampsia using well defined molecular mechanisms.

Keywords: *Tribulus terrestris*; Gokshur; Pregnancy; Preeclampsia; Ayurved

Abbreviations: ACE: Angiotensin-Converting Enzyme; DHA: Docosahexaenoic Acid; DNA: Deoxyribonucleic Acid; IUGR: Intrauterine Growth Restriction; IQ: Intelligent Quotient; LCPUFA: Long Chain Polyunsaturated Fatty Acids; PE: Preeclampsia; RDA: Recommended Dietary Allowance; RNA: Ribonucleic Acid; TT: *Tribulus terrestris*

Introduction

Preeclampsia (PE), a pregnancy-specific syndrome remains a leading cause of maternal and neonatal morbidity and mortality [1]. PE incidence ranges from 3 to 10% of all pregnancies worldwide [2]. Reports indicate that the occurrence of PE is higher in developing countries than in developed countries [3]. Delivery of the baby is the only current cure in PE that inflicts severe prematurity on the baby [4]. PE increases the risk for long-term cardiovascular diseases in mothers and in the offspring [5-8]. It is also evident that children born to mothers with preeclampsia had an increased risk for endocrine, nutritional, metabolic disorders [9]. Growth restricted babies especially born to mothers with preeclampsia are reported to have a lower IQ and reduced adult cognitive performance leading to neurodevelopmental impairment in later life [10-12].

Despite of extensive research on PE worldwide, unfortunately, since the pathogenesisis complex, the precise underlying cellular and molecular mechanisms of PE are unclear [13,14]. Although the precise origins of the disease remain enigmatic, the placenta plays a key role since delivery inevitably leads to rapid recovery suggesting that a hypoxic or ischemic placenta is the trigger of pathophysiology of PE [15,16]. Reports suggest that defective spiral artery remodeling may be the key initiating factor of PE which leads to improper placental perfusion, endothelial dysfunction and fetal growth restriction [17,18]. The hypoxia at the fetal-maternal interface can result in the generation of free radicals leading to increased oxidative stress which will further trigger a wide range of pathophysiological changes in blood and tissues of women with preeclampsia [8,19]. Human studies in our laboratory have shown reduced antioxidants, increased oxidative stress, altered levels of micronutrients (folic acid and vitamin B12) and omega 3 Long Chain Polyunsaturated Fatty Acids (LCPUFA) which were associated with adverse birth outcome in pregnancy complications like PE and preterm deliveries [20-24]. Further, animal studies have shown maternal micronutrient imbalance alters fatty acid desaturasesin dams and increases oxidative stress in the offspring [25-27].

Even though oxidative stress is well established in preeclampsia, supplementation studies with antioxidants like vitamin C and E in preeclampsia are inconclusive [28-30]. A study reveals that antioxidant supplementation to pregnant women with low antioxidant status was associated with better maternal and perinatal outcome [31]. In contrast, a recent review does not support the use of synthetic antioxidants during pregnancy for the prevention of preeclampsia [32]. Further, antioxidant/phytonutrient (vegetable and fruit juice powder) supplementation in early pregnancy did not decrease rates of preeclampsia [33]. There are number of reviews which have evaluated interventions for prevention of preeclampsia which includes antenatal surveillance, modification of lifestyle, nutritional supplementation and pharmacological therapy [34,35]. Despite the variety of possible prophylactic interventions

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Received December 17, 2013; **Accepted** January 04, 2014; **Published** January 12, 2014

Citation: Kilari A, Deshpande M, Joshi S (2014) A Novel Molecular Mechanistic Hypothesis to Validate the Therapeutic Effects of *Tribulus terrestris* (Gokshur) to Ameliorate Pathophysiology and Improve Pregnancy and Fetal Outcome in Preeclampsia. Gynecol Obstet (Sunnyvale) 4: 195 doi:10.4172/2161-0932.1000195

described, studies have produced disappointing results [36]. Interventions such as rest, exercise, reduced salt intake, garlic, marine oil, antioxidants, progesterone, diuretics, and nitric oxide showed insufficient evidence to be recommended as preventive measurements for PE [35]. On the other hand, reports suggest that many traditional herbal compounds possess rich antioxidant properties [37]. However, no reports or reviews have evaluated the effect of traditional herbal interventions in preeclampsia. Thus, at present, there are no well standardized therapeutic means in both modern medicine as well as traditional medicine to ameliorate the pathophysiology of PE and improve pregnancy and fetal outcome. In order to have effective therapeutic strategy for PE, it is essential that use of traditional herbal compounds should be combined with proper micronutrient dietary balance.

Balanced Traditional Herbal Medicines and Dietary Micronutrients

Dietary regimen advised in ayurved during pregnancy

The traditional knowledge of Indian medicinal plants which is inherited from ancestors is very effective, valuable, useful and with fewer side effects than the synthetic pharmacological agents. Ancient Indian traditional medicine known as 'Ayurved' dates back to 3000 B.C and is a holistic system of medicine which encourages the appropriate changes in diet and lifestyle to maintain an individual's health. Ayurved advises the month wise dietary regimen during pregnancy to nourish the mother, to help the growth and development of the fetus, to ensure smooth child birth and to help the secretion of breast milk [38]. This regimen includes food and herbal preparations and are predominantly sweet in taste, easy to digest, cooling to the body and liquid in consistency. During sixth month of pregnancy, Gokshur (*Tribulus terristris*), processed in clarified butter (Ghee), added to gruel (Kanji) and Ghee processed with sweet herbs were advised. Since preeclampsia develops after 20 weeks of gestation (6th month of pregnancy) and Gokshur was also advised during 6th month of pregnancy, it is interesting to explore the efficacy of Gokshur in ameliorating the pathophysiology of preeclampsia.

***Tribulus terrestris* in ayurved:** *Tribulus terrestris* (TT) is known as 'Gokshur' in Ayurved, 'caltrop' in English, 'Gokharu' in Hindi (national language of India). Gokshur has been referred in many contexts in Ayurved classics like Charaksamhita and Sushrutsamhita. TT is aprostate herb, annual/perennial with many slender, spreading branches in all directions and belongs to Zygophyllaceae family. TT is a common weed, springing in waste lands, road sides and in fields soon afterfirst shower. In Ayurved, Gokshur has been indicated in many disease conditions such as cardiovascular (Hridroga), inflammation (Shotha) and to maintain pregnancy (Garbhasthapana) etc. [39]. Clinical studies on Gokshur and its formulations have shown improved sperm count and motility, effective in the treatment of urolithiasis, reduced symptoms scores in benign prostate hyperplasia and improved lipid profile [40-43]. Diuretic action of Gokshur has been studied using rats [44].

Saponins of *Tribulus terrestris*: Several studies have isolated, identified and reported the saponins from the T*T. Tribulus* species are rich source of steroidal saponins and steroidal glycosides [45,46]. Feruloyl amide derivative (tribulusamide C) and Furostanol saponins were isolated from the fruits of *Tribulus terrestris* while steroidal saponins such as protodioscin, tribulosaponin B, metilprotodiostsin, terrestrozin H, prototribestin, gracillin were found from *Tribulus terrestris* [47-49].

Therapeutic activities of TT on various biological systems: There were several reported clinical and experimental studies on different therapeutic actions of TT on various physiological systems which have been systematically reviewed in this paper and compiled according to the biological systems.

Renal system: A very common clinical condition known as urolithiasis (kidney stones) which is due to adhesion of calcium oxalate crystals to kidney cells is associated with severe pain and discomfort in the abdomen. Purified protein biomolecule from TT can be used in kidney stones [50]. TT extract protects kidney against cadmium induced toxicity [51]. Glycolate oxidase (GOX) is one of the key enzymes involved in the pathway of oxalate synthesis and the anti-GOX leads from TT have been reported [52]. Aqueous extract of TT restores kidney tissue in oxidative stress induced rats [53]. A capsule containing TT showed beneficial effect in treating the urolithiasis [54]. In contrast, use of TT to prevent renal calculi induced hepatotoxicity, nephrotoxicity and neurotoxicity in an Iranian male patient [55]. Methanolic extract of TT has shown protective effect on kidney by regulating oxidative parameters [56]. Saponins from TT have inhibited the growth of the renal carcinoma cells [57]. TT has shown diuretic and contractile effects in propelling urinary stones [58].

Reproductive system: TT has long been used as a traditional medicine to treat impotency and improve sexual functions in humans and also treatment with TT has decreased ovarian cysts in polycystic ovary induced rats [59]. Histological study revealed that the testes of fish treated with TT extract contained all stages of spermatogenesis and sperm quality [60,61]. A review on the potential role of plant based antioxidants includes TT to control the oxidative stress induced sperm production and quality in livestock [62]. TT has significantly lowered IPSS scores in the initial treatment of symptomatic benign prostatic hyperplasia [63]. A recent review on scientific validation of traditionally used herbal plants including TT as aphrodisiac herbs for the management of sexual disorder erectile dysfunction [64-66], little evidence in improving female sexual dysfunction and increase in reproduction rate up to two generations [64-68]. A study showed a protective effect of TT against cadmium induced testicular damage and improved the serum testosterone in rats [69,70]. TT has improved sperm production in rats without altering circulating androgens but not able to stimulate endocrine sensitive tissues such as the prostate, seminal vesicle, uterus and vagina in Wistar rats [71].

Hepatic system: TT fruit extract has provided protection against induced hepatic damage in the mice [72]. Ethanolic extract of TT reversed the cadmium induced oxidative stress and changes in hepatic functional markers [73]. TT is protective against cytotoxicity in HepG2 cells and liver cancer cell line [74,75]. TT also showed inhibitory effect on human pancreatic amylase and hypoglycemic effect in mice by inhibiting oxidative stress. TT has also shown antimicrobial and antifungal activity 79 [76-79].

Nervous system: A study supports the protective role of TT in cerebral architecture in dietary induced hyperlipidemia [80]. *In vitro* studies have shown that TT saponin decreases the apoptosis of rat cortical neurons [81]. A formulation containing TT showed both antidepressant and antianxiolytic activity in rats [82]. Baisong tablet containing TT has the antidepressant effect by downregulating CRH mRNA expression in brain [83].

Anticancer activity: Aqueous extract of TT proliferates and induces apoptosis in human liver cancer cells through the inhibition of NF-κB signaling and regulating polyamines' homeostasis [84,85]. TT has shown protective effect against UVB-induced carcinogenesis [86].

Cardiovascular system: Tribulosin, a component of TT has

protective effects on cardiac myocytes via ERK1/2 pathway [87]. Saponins of TT can protect cardiocytes with its effect of resisting oxygen free radical in rats [88]. Saponin of TT has shown preventive effect against myocardial apoptosis [89]. Dietary intake of TT has lowered serum lipid profiles and may partially repair the endothelial dysfunction resulting from hyperlipidemia in rabbits and mice [90,91]. Triterpenesaponin of TT protects cardiocytes during chemical hypoxia-ischaemia *in vitro* [92]. Saponins from TT can relieve the damage of cardiac muscle cell and attenuate the ventricular remodeling after myocardial infarction [93].

Antihypertensive effect: A clinical study has showed antihypertensive effect of TT without any side effects suggesting that TT can be safely recommended for a longer period to the patients of mild to moderate hypertension mainly associated with fluid retention [94]. Antihypertensive effect of TT and a negative association between TT consumption and ACE activity have been reported in rats [95,96].

Antioxidant activity: Aqueous extract of TT has attenuated neuropathic pain by regulating oxidative stress markers in diabetic neuropathic pain model [97]. TT extract has shown considerable anti-oxidant potential [98]. Crude extract of TT showed antioxidant and antimicrobial properties *in vitro* [99]. Aqueous extract of TT has reduced tumor incidence and number of papillomas in mice by decreased lipid peroxidation levels and increased glutathione levels in the liver [100]. TT saponin, ingredient of Xinnao Shutong capsule, revealed the protective effect against cerebral ischemic injury by reducing malondialdehyde levels [101]. TT showed potent inhibition of COX-2 activity [102].

Rationale of Gokshur in the treatment of preeclampsia: Extensive literature review on TT suggests that TT is effective in treating many disease conditions through its rich antioxidant activity [97,88]. It is evident that TT have antihypertensive and antioxidant effect and preeclampsia is known to be associated with broad range of pathophysiologies particularly hypertension and oxidative stress. This makes TT a preferred herbal agent for treatment of PE. However, there are no studies on TT interventions during pregnancy in reducing the risk of preeclampsia. Therefore, there is a need to explore the effect of TT in ameliorating the preeclampsia symptoms using animal models followed by clinical trials. Furthermore, it is important to have a molecular mechanistic hypothesis to validate its efficacy.

Micronutrients in one-carbon metabolism–risk for adult disorders in the offspring

Maternal micronutrients like folate and vitamin B12 play key role in one-carbon metabolism. Folate (B9) is a water soluble vitamin and involved in DNA synthesis during embryonic and fetal development [103], maintains adequate cellular levels of S-Adenosylmethionine (SAM) known as a methyl donor required for biological methylation [104]. Disruption of folate-mediated one-carbon metabolism is associated with many pathologies and developmental anomalies [105]. Vitamin B12 (cobalamin) is required for cellular metabolism and is essential during pregnancy because of its role in DNA and methionine synthesis. Cobalamine deficiency leads to hematological (megaloblasticanaemia), neurological (tingling and numbness of the extremities) and cognitive disturbances (gait abnormalities, visual disturbances, memory loss and dementia) [106]. Recent review has mentioned that low maternal vitamin B12 status is associated with increased risk of neural tube defects and poor offspring cognitive functions [107]. Hence, both folate and vitamin B12 are necessary for fetal development and the deficiency of these micronutrients is associated with multiple disorders. The deficiency of folate and vitamin B12 raise the concern for the community at large, more specifically neonatal and child health [108].

Indian studies have reported lower dietary intakes of micronutrients such as calcium, Iron and folate well below the Indian RDA and also lower micronutrients (vitamin B12) status in Indian pregnant women [109,110]. Further, both maternal and fetal vitamin B12 levels in Indians were lower than that reported in western subjects [111,112]. In developing countries, diets are generally low in animal products and consequently in vitamin B12 content which may cause reduced fetal growth [113]. Further, most of the Indians are being vegetarians; a high prevalence of vitamin B12 deficiency in early pregnancy among urban South Indian women was reported [114]. Children born to mothers with a lower vitamin B12 status have shown a reduced cardiac sympathetic activity [115]. Another Indian study has revealed that the two thirds of the mothers had low vitamin B12 concentrations and high circulating concentrations of homocysteine in IUGR [110]. Vitamin B12 is essential in homocysteine metabolism and hyperhomocysteinemia is associated with preeclampsia. Evidences clearly suggest that the prevalence of vitamin B12 and folate deficiency is high in the Indian population [116]. Although a National program of prenatal Iron folic acid supplementation is in operation for over 30 years in India, micronutrient status did not improve in Indian pregnant women due to inadequate antenatal care [117]. Further, large dose (3-5 mg) of folic acid per day was given118 as compared to folate RDA (400-500 μg/day) for pregnant women [118,119]. High folate in the presence of lower vitamin B12 may affect the one–carbon metabolism leading to epigenetic changes and increase the risk for adult diseases.

Several studies in our laboratory on both human and animals regarding the role of maternal micronutrients and DHA in one-carbon metabolism and their association with adverse birth outcome in pregnancy complications have been reported. For instance, the associations of folic acid, vitamin B12, homocysteine with DHA and baby weight during pregnancy in humans [24]. Further, animal experiments have shown the effects of maternal micronutrients imbalance during pregnancy on maternal fatty acid desaturases & transport proteins; and offspring brain oxidative stress and antioxidant enzymes [25-27]. A hypothesis has been proposed that altered maternal micronutrients will increase homocysteine and oxidative stress leading to pregnancy complications and adverse birth outcomes and result in epigenetic programming of adult diseases in later life [22,23]. Epigenetics is defined as changes in gene expression which are not caused by changes in DNA sequence1 [120]. This epigenetic regulation is examined by 4 main modes i.e. DNA methylation, imprinting, histone modification, and small RNA-mediated control, specifically miRNAs [121]. A recent study has shown altered DNA methylation in placental angiogenesis in preeclampsia [122]. The above evidences clearly indicates that factors like altered maternal micronutrients, omega 3 fatty acids, increased homocysteine and oxidative stress are involved in the pathology, epigenetic changes and fetal programming in preeclampsia. Despite essential role of maternal micronutrients (folate and vitamin B12) in pregnancy, studies on supplementation with micronutrients during pregnancy are controversial. Studies with daily consumption of either 400 μg or high doses of folic acid during early pregnancy could not prevent the occurrence of gestational hypertension and preeclampsia [123,124]. In contrast, supplementation of multivitamins containing folic acid in the second trimester has shown the association with reduced risk of preeclampsia [125]. A recent report has been demonstrated the association between folic acid supplementation and oxidized low-density lipoprotein which effects oxygen free radicals during pregnancy and are a risk factor for preeclampsia [126]. Maternal RBC folate

concentration in early pregnancy is associated with small for gestation age and preterm births, but not with preeclampsia [127]. Furthermore, Indian cohort has shown reduced micronutrients and antioxidant enzymes which were associated with oxidative stress in preeclampsia [128]. A recent review explains that maternal macronutrients deficiency plays an important role in fetal programming in developing countries leading to insulin resistance, glucose intolerance, hypertension and adiposity in adulthood [129]. Research on epigenetics started focusing on prenatal supplementation and their epigenetic changes during embryonic development [130]. However, there are no studies on prenatal herbal (antioxidant rich) supplementation and epigenetic regulation of antioxidant genes which are major contributor in pathology of preeclampsia. Therefore, it is important to explore the efficacy of herbal agents (natural antioxidants) along with micronutrients during pregnancy in ameliorating preeclampsia and reduce the risk of adult disorders in the offspring.

Hypothesis

We hypothesize that the well standardized use of TT or formulations of TT with micronutrients in preeclampsia may ameliorate the symptoms of preeclampsia primarily due to its high antioxidant potential, improve the birth outcome, control the epigenetic changes and reduce the risk of adult metabolic and behavioral disorders in the offspring.

Conclusion

In summary, micronutrients deficiency, hyperhomocysteinemia leading to oxidative stress are implicated in the pathology of preeclampsia and fetal programming of adult diseases. However, supplementation with micronutrients/synthetic antioxidants during pregnancy showed controversial results. Further, there are no reported studies on supplementation with antioxidant rich Ayurved herbal agents in preeclampsia. Ayurved has mentioned multiple therapeutic effects such as cardioprotective, anticancer, neuroprotective, hepatoprotective, renal and aphrodisiac etc. of TT and several clinical and experimental studies have well established and validated the beneficial effects of TT including its antioxidant and antihypertensive activities. However, no study has examined the effect of TT in the prevention/treatment of preeclampsia. Therefore, there is a need to explore the efficacy of TT along with micronutrients in the treatment of preeclampsia and regulation of epigenetic changes in preeclampsia. Hence, future studies should investigate the efficacy of TT along with micronutrients in the treatment of preeclampsia using well defined molecular mechanisms.

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Citation: Kilari A, Deshpande M, Joshi S (2014) A Novel Molecular Mechanistic Hypothesis to Validate the Therapeutic Effects of *Tribulus terrestris* (Gokshur) to Ameliorate Pathophysiology and Improve Pregnancy and Fetal Outcome in Preeclampsia. Gynecol Obstet (Sunnyvale) 4: 195 doi:10.4172/2161-0932.1000195