



# Probable Mode of Action of *Sita kasmaryadi* Herbal Decoction in Placental Compliance – A Review

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## Abstract

The occurrence of IUGR (Intra uterine growth retardation) is estimated to be approximately 5% in the population and it is considered as the third leading cause for perinatal mortality in India. Despite plentiful management options, none is effectively proved in improving placental circulation and foetal weight gain. Indian medicine practices a herbal decoction with *Glycyrrhiza glabra* Linn., *Gmelina arborea* Roxb. ex. *Smith* and sugar. The pharmacological potentials of this decoction was attempted to explore here in this review based on available researches. Thorough internet search was performed to derive the data. Recent researches on detailed chemical composition and its possible pharmacological action also had been detailed. It is an effective formulation in improving placental and umbilical cord circulation, aids in improving foeto-placental circulation to a greater extent with negligible side effects.

**Keywords:** Kasmaryadi Decoction, Upavishtaka, Sushkagarbha, IUGR

## 1. Introduction

Foetal retardation is considered as the third leading cause for perinatal mortality in India<sup>1</sup>. Numerous attributing factors like environmental, physical, social etiological factors are involved in the high prevalence of developed countries like India<sup>2</sup>. The occurrence of IUGR is estimated to be approximately 5% in the population. Infants who weigh less than 2500 g at term possess a 5-30 times high risk of perinatal mortality. The mortality rate is 70- 100 times higher in infants who weigh less than 1500 g. Aetiological factors of IUGR can be listed as maternal, foetal and placental. Maternal factors include reduced utero placental flow, reduced oxygen carrying capacity, systemic conditions like diabetes mellitus, hypertension. Reproductive age is also an important factor influencing the growth of the foetus. Women residing in high altitude places may suffer from hypoxia. Similar environmental factors possess a definite role in the growth of the foetus. Maternal habits like smoking had a negative impact<sup>3</sup>. Significant foetal factors are genetic abnormality, congenital malformations and infections. Placental causes are of prime importance in

IUGR. Any defects in placental circulation and abnormal placental presentations like placenta previa comprises placental factors<sup>3</sup>. Placental ischemia has a major role in the pathogenesis of IUGR as it prevents the transfer of adequate amounts of glucose and nutrients to the foetus. When there is a negative maternal-foetal glucose gradient and glucose insufficiency to meet the needs of the foetus, endogenous Hepatic Glucose Production (HGP) is activated<sup>4</sup>. However, foetus with IUGR due to placental insufficiency always have an early activation of HGP. Moreover, activated HGP is resistant to suppression by insulin. Abnormal maternal vascular under perfusion along with low placental weight are among the common pathologies seen with foetal growth retardation. Likewise, foetal thrombotic vasculature, umbilical cord anomalies and chronic villitis are also main factors<sup>5</sup>. Despite plentiful management options, none is effectively proved in improving placental circulation and foetal weight gain.

Key investigations for the condition includes ultra sound scan and determination of a foetal protein (alpha-fetoprotein) in mother's blood. Diagnostic criteria of IUGR consists of level 1 evidence of pregnancy dating, estimated foetal weight below 3% using locally accepted

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growth curve and absent/reversed end diastolic flow of the umbilical artery Doppler. There are no effective management for IUGR in Modern fraternity. Still they are administering amino acids, low dose aspirin, plasma volume expansion measures and ante natal steroids. Ante natal administration of steroids results in developmental irregularities of lung, brain and heart<sup>6</sup>.

Ancient Indian systems of medicine, Ayurveda provides efficient remedy for this condition. Upavishtaka (improper growth of foetus), Nagodara (Dessication of foetus) and Garbhasosha (growth retardation) are related conditions explained in Ayurveda. Upavishtaka (improper growth) is caused by the use of pungent and hot articles that are contraindicated in pregnancy. Pitta and Kapha gets blocked due to the aggravated Vata. This causes obstruction to the channels that supply nutrition to the foetus causing growth retardation in the same way as the paddy does not grow properly if the water does not reach field due to obstruction with leaves and grasses to the channels. Nagodara also results from frequent fasting and use of other vatha vitiating articles. Garbhasosha is the emaciation of foetus due to improper nutrition or vaginal discharges. Vata is vitiated in this condition. All these conditions differ in aetiological factors and dosha associations. Eventhough Vatha is the predominant dosha in these conditions, Upavishtaka and Garbhasosha shows association with either Pitha or Kapha<sup>7</sup>. There are various month-wise milk decoction formulations for healthy pregnancy explained in traditional Ayurvedatexts<sup>8</sup>. *Sitakasmaryadi* decoction is a different formulation, indicated specifically in an abnormal pregnancy condition and it contains *Yashtimadhu* (*Glycyrrhiza glabra* Linn.), *Kasmari* (*Gmelina arborea* Roxb. ex. Smith) and sugar, that is processed in milk so that the fat-soluble active ingredients of the formulations are being extracted in to the preparation<sup>9</sup>. This combination is well explained in the treatment of Vatha vitiated conditions in the treatise of *Ashtangahridaya*. The formulation has indication in growth retardation, possibly dosha. The decoction proved its efficacy in clinical practice. A 30-year-old patient who was presented with Placenta Previa grade-3 had underweight foetus (1kg), at 32 weeks USG. She had no history of hypertension or diabetes or any other abnormalities. Here the patient was presented with Pitha vitiated signs like burning sensation all over the body and heart burn. Hence the condition was taken as Upavishtaka with Vatha-Pitha association. She was prescribed with *Sita kasmaryadi* decoction two times a day for 2 weeks along with normal diet pattern and rest. After 2 weeks the USG was repeated and foetus showed marked improvement of 800 g. The medication was continued until c-section

which was fixed after 1 week and 3 days. Birth weight of the foetus was 2.3 kg.

Objective of this review was to analyse the possible mode of action of *Sita kasmaryadi* decoction based on available literature. It will be interesting to the scientific world to know how this simple combination of two herbs alleviating the said condition.

## 2. Mechanism of Placental Compliance

Placenta is an organ for conveyance of all essential nutrients and metabolic wastes between maternal and foetal part. Placental blood flow and vasculature are two vital aspects for a healthy functioning placenta during gestation. Similar to maternal stress, various factors contribute to the raised placental resistance<sup>10</sup>. High insulin resistance, placental abnormality, vascular anomalies are few among those factors. These can be inferred in gestation from uterine artery pulsatility and umbilical artery resistance indices with the help of umbilical artery Doppler velocimetry<sup>11</sup>. Blood in placenta or umbilical artery needs to overcome some sort of resistance to flow inside and that refers to placental resistance affecting the placental passivity. Normally as gestation advances, resistance decreases to meet all the nutritional demands<sup>12</sup>. In some occasions placenta fails to relax the resistance over the microvasculature already exerted leads to placental ischemia or insufficiency and this is proved as the leading cause of IUGR in a study conducted on sheep<sup>13</sup>. Likewise, when any abnormality occurs to placenta, its resistance will increase remarkably in the microcirculation of placenta. End diastolic flow is a tool to assess the foetal stress in any stage of gestation. It should be same in 14 weeks and 28 weeks in normal cases<sup>14</sup>. Maldevelopment and decrease in the number of peripheral villi results in increased resistance and reduction of end diastolic flow. Experimental studies in sheep proved that treatments increase the placental blood flow and can cure foetal growth retardation<sup>15</sup>. As a consequence, a concept of placental blood flow and vascular development are evolved as therapeutic targets<sup>16</sup>.

## 3. Appraising Potentials of *Sita kasmaryadi* Decoction

*Sita kasmaryadi* is part of an age old tradition, widely used in the management of intrauterine growth retardation. The lipid and water soluble constituents are extracted in the decoction as it is prepared in milk and water.

*Glycyrrhiza glabra* Linn. and *Gmelina arborea* Roxb. ex. Smith are taken in equal amounts along with sugar to taste. *Sita kasmariyadi* has very noble palatability also. Milk decoction is prepared with drugs, milk and water in the ratio of 1:4:16. For that 6 gm of each drug should be taken. The formulation is cooked in low flame and reduced to 48 ml. The decoction is administered in two divided doses of 24 ml in the morning and evening for 3 weeks.

*Glycyrrhiza glabra* Linn. is famed for its various chemical constituents and thereby numerous pharmacological properties. Water soluble extract of the drug yields 8 saponins, named glycyrrhizin or glycyrrhic acid, 5 types of licoricesaponins, araboglycyrrhizin and apiglycyrrhizin. It entails of a flavanone named bisdesmoside. Onionin, 3isoliquiritin compounds, 2 liquiritin compounds and licuraside are flavonoid glycosides yielded from *Glycyrrhiza glabra* Linn. Virtually 58 phenolics are found in the drug<sup>17</sup>. However, ethyl acetate soluble fraction of the drug brings forth 3 chalcones, 4 flavanoids, 3 isoflavanoids and 4 pterocarpanes based on researches. Besides, glabridin is found to be present in *Glycyrrhiza glabra* Linn. species and which is absent in the other species. Structural formula of all the compounds are elucidated and are available<sup>18</sup>. In Ayurveda, the underground stem or rhizome is used for making different formulations. Glycyrrhizin content varies significantly with underground horizontal stem, underground vertical stem as well as roots. The glycyrrhizin content decreases considerably in *Glycyrrhiza glabra* Linn. root that grown in depth more than 300 m. Therefore, it is proved that thinner rhizomes encompass highest aggregate of glycyrrhizin<sup>19</sup>.

Vasorelaxation activity of *Glycyrrhiza* species is proved in phenylephrine pre-treated contracted endothelium. Glabridin is a vasorelaxant dependent on potassium channels<sup>20</sup>. Glycyrrhizin is 30 times sweeter than sucrose and effective in lowering blood glucose, insulin and lipids. It also has a protecting effect on advanced glycation end products induced endothelial dysfunction. 18 $\beta$ -glycyrrhetic acid, a major metabolite of glycyrrhizin absorbs in to blood as such and reaches the brain crossing the blood brain barrier<sup>21</sup>. *Glycyrrhiza glabra* Linn. possess an affinity towards glucocorticoid receptors based on researches<sup>22</sup>. The 8 isoforms of glucocorticoid receptors were found in pre term placenta with different expression<sup>23</sup>. These references give glimpses of affinity of the drug towards placenta.

*Gmelina arborea* Roxb. ex. Smith. is a well-known herb used in Indian medicine. It is widely seen in the reserve forest and Western Ghats of Kerala. Its wood is

also used for timber purposes. It possesses a variety of active ingredients from stem bark, root bark, fruits and leaves. Fruit is being used in this formulation. Fruiting occurs during the month of May-June. We had collected the ripe yellow coloured fruit in June with fruity smell. It also possesses alkaloids, anthocyanins, mucilages, leucoanthocyanins and saponins as active ingredients<sup>24</sup>. Stem bark extract showed vascular relaxant activity on pre-contracted aortic rings. The herb acts through flavonoids from the functional endothelium or directly on the smooth muscle cells. Flavanoids are good antioxidants which are having active role in the defence system and also holds stability from osmotic variation in erythrocytes<sup>25</sup>. Diuretic effect of the fruit extract was comparable to the standard drug. Apigenin, arboreol, gmelinol and tartaric acid are some of the other active ingredients in the herb. Apigenin is a most commonly seen active bio flavonoid with potent anti-oxidant, anti-diabetic and anti-hypertensive properties<sup>26</sup>. Apigenin had been quantified from the dried root powder of *Gmelina arborea* Roxb. ex. Smith. Apigenin found to inhibit TGF-beta1 induced expansion of pre contracted alpha-smooth muscle actin, positive myrofibroblast. It also reduces agonist induced vascular contraction regardless of endothelial function. Aqueous bark extract holds regenerative effect of beta cells of pancreas in diabetic rats<sup>27</sup>.

### 3.1 Synergistic Action of the Formulation

*Sitakas maryadi* decoction possess herbs which possess Guru (heavy), Snigdha (unctuous) and Seetha (cold) and sweet in taste. Pharmacologically it alleviates Vatha by its sweet taste, heavy and unctuous nature and alleviates Pitta by virtue of its sweet taste and cold potency. Therefore, *Sitakas maryadi* decoction alleviates IUGR with Vatha and Pitta association<sup>28</sup>.

Both the herbs acts synergistically to achieve a noble pharmacological effect. *Glycyrrhiza glabra* Linn. was shown to possess a hypertensive effect in continuous usage whereas *Gmelina arborea* Roxb. ex. Smith is a strong anti-hypertensive herb. *Glycyrrhiza glabra* Linn. and sugar combination may upsurge the blood sugar in gestation which may turn harmful. On the other hand, *Gmelina arborea* Roxb. ex. Smith is potent enough to neutralise the hyperglycaemic effect of the combination. Table sugar is a rare component in herbal decoctions. The table sugar added aids in improving the palatability and effecting some pharmacological action. Fructose will stimulate the production of hyaluronic acid through certain pathways, which is an important glycosaminoglycan in the gravid uterus<sup>29</sup>. Healthy umbilical cord is another important factor that influence the weight gain of foetus.

Connective tissue that surrounds and provide protection is known as Whartons Jelly (WJ). WJ acts like a vessel that has significant role in foetal growth by playing a role in foetal nutrition and aiding the foeto-placental circulation<sup>30</sup>. The complete absence of WJ amounts to foetal death. It has also been proved that the umbilical cord diameter and anthropometric features are directly related to each other<sup>31</sup>. In contrast, the area of WJ and lumen of umbilical artery is not related to the foetal weight gain<sup>32</sup>. It is obvious that the content or quality of WJ should be maintained for proper foetal weight gain. Another factor that influence the mechanical characters of umbilical cord is the decline of hyaluronic acid. This is an important abnormality of umbilical cord leading to anoxia and IUGR in foetus<sup>33</sup>. *Gmelina arborea Roxb. ex. Smith* fruit consists with magnificent amounts of amino acids that can provide nourishment for the foetus and thereby effective in the decline of hyaluronic acid.

#### 4. Discussion

An herbal decoction with *Glycyrrhiza glabra* Linn. *Gmelina arborea Roxb. ex. Smith* and sugar constitutes an effective remedy for IUGR in Indian medicine with unreported side effects. Nowadays health researches points out to the significance of placental circulation and vasculature as targets for IUGR medicines. Ayurveda, is an age old tradition with centuries of glorious heritage as herbal medicine. While analysing the possible pathways of these formulations based on available researches, some fascinating aspects can be drawn out. *Glycyrrhiza glabra* Linn. and *Gmelina arborea Roxb. ex. Smith* are potent smooth muscle relaxants as proven by experimental studies<sup>34,35</sup>. That can impart a greater lumen for placental arteries and relaxation to the resistance with the circulation. On the other hand, the fructose content from *Glycyrrhiza glabra* Linn. and sugar, may trigger the production pathway of hyaluronic acid which is the main ingredient of WJ. Hence maintaining the quality of WJ offers protection to the umbilical cord and good flow of circulation through umbilical vessels<sup>36</sup>. The adverse effects of *Glycyrrhiza glabra* Linn. on continuous usage are the hypertensive and hyperglycaemic effects which could make a negative impact on gestation is clearly nullified with the opposite qualities of *Gmelina arborea Roxb. ex. Smith*<sup>37</sup>.

#### 5. Conclusion

This review is an attempt to explore the pharmacological effects of a herbal decoction being used for centuries.

*Sitakas maryadi* decoction can be effective in conditions of IUGR. More researches have to be undertaken in this regard for utilising the cost effective benefits of herbal medicine. There are stringent ethical rules for such researches to conduct. It is one of the major hurdle inclinical trials for gestation. More over effective researches in these types of formulations can be a boon for the mankind.

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