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Phthalate and ovarian physiology: A brief review of therapeutic potential of Shatavari (*Asparagus racemosus*)

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Abstract
Shatavari (*Asparagus racemosus*) root extract has been used as herbal reproductive tonic in traditional as well as ayurvedic systems of medicine for a long time. The molecular mechanism by which shatavari regulate female reproductive health remains poorly understood. Studies carried out on experimental mammals suggest that bioactive gradients (sarsasapogenin and shatavarin I-IV) of shatavari decreases generation of reactive oxygen species (ROS) and reduce oxidative stress in ovarian follicles. Further, herbal plants based scientific research suggests that medicinal herbs have the ability to regulate estrogen or progesterone levels and may accountable to maintain reproductive health. In other hand, the increased levels of ROS and oxidative stress due to exposure of endocrine disruptors like phthalates may affect follicular occyte and its associated cells by damaging cellular DNA. The granulosa cells as well as oocyte apoptosis within the follicular microenvironment deteriorate oocyte quality. Poor quality of oocyte directly affects fertilization, implantation and pregnancy rates and increases abortion rate. Thus, based on existing animal as well as human studies, we are in belief that bioactive ingredients of shatavari could be used as herbal female revitalize agent to cure various incurable reproductive abnormalities

Keywords: Shatavari; Reactive oxygen species; Granulosa cell; Oocyte; Apoptosis; Fertility

1. Introduction
Ovarian folliculogenesis is a very complex process in which approximately 99% of follicles undergo follicular atresia and only few follicles reach to the ovulatory stage**.** During this process, any functional disruption may lead to reproductive problems which ultimately affect the reproductive potential of an individual. Interestingly, it is reported that several type of environmental factors including endocrine disruptors has the potential to target the ovary at all stages of development [1-4]. It may affect the female reproductive development including early puberty, causes delay in menstrual cycle, and poses infertility even at low levels of exposure which could extend to future generations. The interruption during follicular development due to increased level of reactive oxygen species (ROS) and oxidative stress may lead to spontaneous resumption of meiosis. Although any type of oxidative damage at the level of DNA lead to death of encircling granulosa cells, and subsequently oocyte becomes more susceptible towards cellular apoptosis [4, 5]. This is supported by observations that granulosa cells are more susceptible towards oxidative stress-mediated apoptosis as compared to oocytes. The healthy ovarian granulosa cells are necessary not only for produces estrogen hormone (by aromatase 450 activity) but also it help oocyte to achieve meiotic competency to develop right female gamete for various assisted reproductive technology programs.
It has been seen that endocrine disruptors like phthalate directly acts on ovarian granulosa cells and thereby inhibit estradiol production by blocking estardiol receptor in mammals that leads to increase oxidative stress and ovarian somatic cell apoptosis [6-7]. If so, it is a serious concern for public health because phthalate like compounds adversely affect the two essential ovarian processes like folliculogenesis and steroidogenesis which are essential to maintain fertility. However, we still have limited information about the impact of phthalate like compounds and their mechanism by which it exerts ovarian toxicity in women and in animal models. Thus, future studies are needed to understand the mechanism of action of phthalates in mammalian system.
Oocyte is one of the most important factors that directly affect reproductive health of a female. It is believed that DEHP may induce its toxicity in two ways; either by disturbing the levels of some hormones like estrogen or progesterone and thus reduces fertility probably by inhibiting follicular development or by inducing oxidative stress via reactive oxygen species (ROS)

generation and hence decreases the fertility. ROS are known to play important roles in many physiological processes [8-9]. It has been reported that oxidative stress may be an important mechanism underlying the toxic effects of phthalates [10-11]. Ambruosi *et al.* [12] reported that phthalate like compound DEHP induces ROS generation and alters oocyte maturation suggesting the role of DEHP-mediated ROS involvement in the ovarian physiology. These results suggest that DEHP-mediated ROS generation might be one of the mechanisms underlying the inhibition of the process of ovarian folliculogenesis and steroidogenesis, and in turn, the reproductive toxicity of DEHP. Unfortunately, there are no remedies to cure or minimize DEHP induced reproductive toxicity. Hence, it is important to search herbal-based reversible medicine that are easily acceptable and show minimal side effects with 100% efficacy.

In India, Ayurveda is one of traditional medicinal system that uses herbs from Vedic period to till date for the treatment of various kinds of diseases. Traditional Ayurvedic medicines still play a vital role in rural areas because of their easy access and are economically cheap. Therefore, traditional herbal medicine can be considered to provide holistic treatment and could be one of the better alternative approaches to cure or at least minimize the toxicity of phthalates.

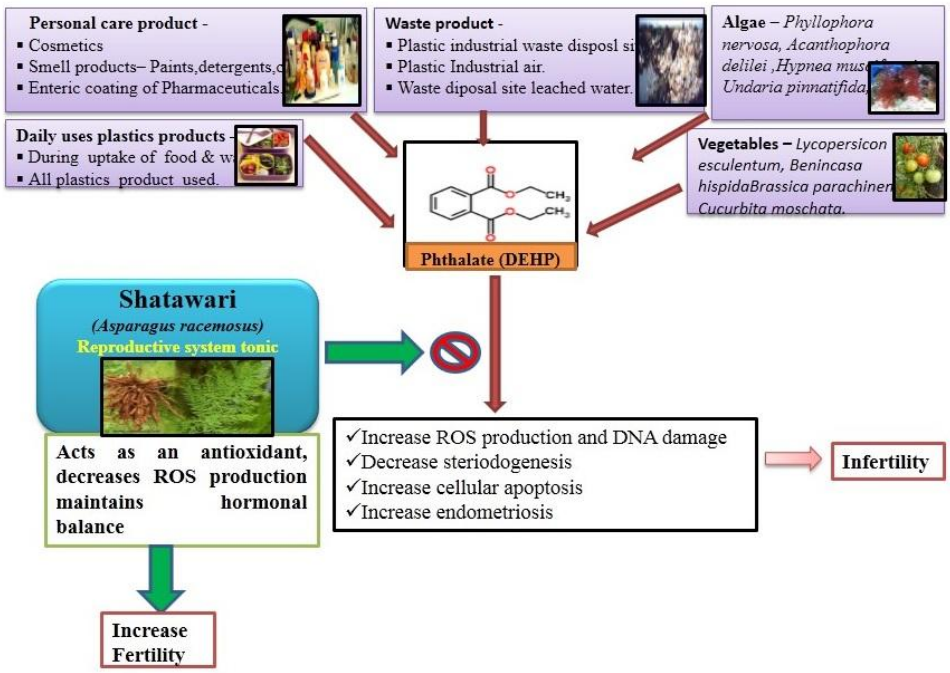

Figure 1. Beneficial effects of Shatavari (*Asparagus racemosus)* on women's health.

Asparagus racemosus (Shatavari; family- Asparagaceae, Liliaceae) is a climbing plant which grows in low forest areas throughout India. The plant is popularly known as 'shatavari' which means 'who possesses hundred husbands or acceptable to many' [13] implying its ability to increase fertility and vitality. In the Indian Ayurvedic system of herbal medicine, this amazing herb is mentioned as the "Queen of herbs", because it promotes love and devotion. Various parts of shatavari are used for treatment of several diseases in traditional as well as ayurvedic systems of medicine globally. The aqueous extract of shatavari root has been used to control ammenorrhea, dysmenorrhea, dysfunctional uterine bleeding [14-15] and gonorrhea [16]. *Asparagus racemosus* also works as a stimulant of endometrium and ovarian tissues, regulate menstruation and ovulation, balance hormonal levels (TSH, FSH, LH, estrogen) and improves the Conception rate (64% vs 28%) in women [17].

Asparagus racemosus is considered as a therapeutic agent because it contains glycosides, diosgenins, cytoestrol and stigmaestend. The major active constituents of *A. racemosus* are steroidal saponins (Shatavarins I-IV) that are present in the roots. The presence of sarsasapogenin and shatavarin I-IV in roots, leaves, and fruits of Asparagus species make this herb an amazing therapeutic agent and it could be useful against reproductive toxicity induced by phthalates. However, there is a need to conduct clinical trial and proper validation to justify the therapeutic candidature of *A. racemosus* against phthalates induced reproductive toxicity. In Ayurveda, it is described that long term use of *A. racemosus* is absolutely safe, as well as even during pregnancy and lactation. Experimentally, it is proved that systemic administration of higher doses of *A. racemosus* extracts does not produce any abnormality in behavior of mice and rat [18]. Furthermore, Prabha *et al.* [19] assessed the safety level of A. racemosus by studying acute and chronic toxicity (1g/kg) on pre and post natal developments in rats and reported that no changes in general behavior, gait, food and water intake on the body weight. Further, lactogenic effects of *A. racemosus* has been investigated in different mammalian species like guinea pigs [20], goats [21], buffaloes [22], including humans [23] and reported that it significant increases milk yield in these species. In recent past, it has been shown that liposomes made from the extract of *A. racemosus* possess huge anti-inflammatory activity and can be utilized for transdermal drug delivery [24]. On the basis of available literature it seems that *A. racemosus* possesss great potential to inhance the mechanism by which shatavari acts at the level of ovarian follicles are remains unclear. Studies using experimental mammals suggest that shatavari root extract enhance secretion of estogen hormone thereby induces folliculogenesis and antrum formation (Kumar *et al*. 2001). Further, it is postulated that shatavari decreases ROS production and helps to increase intercellular communication between cells. The increase level of ROS induces overexpression of p53 and Bax proteins. The increased Bax expression modulates mitochondrial membrane potential and induces cytochrome c release. Increased

cytochrome c concentration induces DNA fragmentation and granulosa cell apoptosis and finally may lead to infertility. The granulosa cell apoptosis reduces estradiol 17-β level required for development and maturation of oocytes in the ovarian follicles. The hypo-estrogenic condition may affect development and maturation of oocytes and trigger apoptosis. Studies from our laboratory suggest that shatavari root extract protect the granulosa cell death by lowering ROS level and inducing estrogen hormone level in rat model (unpublished observation).

Conclusion

Phthalate is frequently used for packing food items and is a major constituent of the polythene. Higher level of phthalate in the circulation may affect the ovarian physiology. Here we propose that shatavari and its bioactive ingredients may useful for the treatment of UT infections, nausea associated with pregnancy, and lactation issues in human. The antioxidant and inducing estrogen hormone secretion properties of shatavari makes it a potential candidate for the development of reversible herbal medicine. Figure 1 summarizes the beneficial effects of shatavari on women's health. This review may spread awareness about the harmful effects of plastic products and the use of cost-effective and cheap herbal medicine to overcome the phthalates-induced reproductive problems in comparison with the costly ART procedures.

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Conflict of interest: None of the author has any conflict.

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