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A REVIEW OF IRANIAN MEDICINAL PLANTS WITH TERATOGENIC AND ABORTION-INDUCING SIDE EFFECTS

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ABSTRACT: Compounds with teratogenic effects can cause genetic defects during pregnancy and subsequently lead to unwanted abortions. Unwanted abortions and postnatal genetic defects can impose economic and psychological burden on the community. This systematic review was conducted to report medicinal plants with teratogenic and abortion-inducing side effects that are used in Iran. To conduct this systematic review, all articles specifically on the teratogenic and abortion-inducing effects of Iranian medicinal plants were retrieved from the Institute for Scientific Information (ISI) and PubMed and their findings evaluated. Many plants have been reported to display teratogenic and abortion-inducing effects, but a limited number of them were experimentally examined and demonstrated to have such effects. Certain plants such as Perovskia abrotanoides and Lawsonia inermis can simultaneously exert teratogenic and abortion-inducing effects. Plants and their derivatives can cause teratogenic effects and lead to unwanted abortion through several action mechanisms. Such plants cannot be considered harmless solely because they are natural; therefore, they should be used during pregnancy cautiously, under physician's supervision, and at specific doses.

INTRODUCTION: Excessive and irregular use of drugs during pregnancy can have adverse effects on fetus ¹⁻⁵. Meanwhile, excessive use of medicinal plants can cause toxic effects on the fetus ⁶. There are no definite or specific guidelines for use of most plants or nature-based products in many countries, while such substances can cause adverse effects on either pregnant women or fetuses ⁷.



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Besides that, there is scant evidence on the side effects due to use of the medicinal plants and nature-basedproducts during pregnancy ⁸. Birth defects represent one of the dangerous side effects of herbal drugs mainly due to misconception that using such drugs is harmless. Declined quality of life, stigma, adverse effects on social relationships, psychological diseases and pressure are some of the consequences of birth defects experienced by parents and affected children ⁹⁻¹³. In 2013, an estimate of 22.9 billion dollars was spent on hospital stays due to birth defects in the USA ¹⁴. In addition, some plants can cause abortion and even endanger maternal health in some cases ¹⁵ such that some mothers may experience certain problems such as psychological

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trauma, anxiety, emotional problems, declined life satisfaction, and depression after unwanted abortion ¹⁶⁻¹⁸. Indeed, some users may be unaware of the abortive effects of these plants, and no information on the medicinal plants is usually provided for physicians. Therefore, having inadequate knowledge about this field has caused numerous problems among women who have spent tremendous costs on pregnancy or are planning for pregnancy ^{19, 20}.

This systematic review was conducted to report medicinal plants with teratogenic and abortive side effects that are used in Iran. To achieve this purpose, the articles on the prevention of serious side effects related to pregnancy, published in reliable journals, were examined.

Search strategies: To conduct the review, Anomaly, Malformation, Birth defect, Teratogen, Miscarriage, Abortion, and Stillbirth combined with Medicinal plants, Herb, and Phyto were used to search for relevant publications indexed in the Institute for Scientific Information (ISI) and PubMed. After identifying accessible articles and abstracts as well as other obtained references, we examined those publications that examined mainly the teratogenic and abortive properties of Iranian medicinal plants. The references without citation were excluded from the review.

RESULTS: Only 19 articles in PubMed and 41 articles in ISI were retrieved of which 27 were indexed in both databases. Further study of the articles indicated that 36 articles should be examined. After the study of the abstracts and full texts of the article, eight articles were excluded because they did not mainly address the purpose of this review. In addition, six studies investigated the plants that were reported to have no teratogenic and abortive effects. In some of the articles published in reliable databases, certain plants such as Elaeagnus angustifolia L. ²¹, Peganum harmala L.²², and Carthamus tinctorius L.²³ were reported to exert teratogenic effects and some other plants such as Peganum harmala L. 24, 25 and saffron 25, 26 demonstrated to cause abortive effects. However, a few number of studies were conducted mainly to investigate the effects of these plants and their derivatives.

Plants and phytochemicals with teratogenic side effects:

Lavandula officinalis: A study investigated the rate of bone anomalies due to antiepileptic drugs and L. officinalis comparatively. This study demonstrated that both the essential oils of this plant and phenytoin caused femoral and tibial abnormalities and affected other growth factors negatively, and finally increased the number of abnormal fetuses in mice, but the side effects induced by phenytoin were much more severe than those due to L. officinalis 27 .

Lawsonia inermis: The pulverized dried leaf of L. inermis is used as a cosmetic product in Iran. Seven-day administration with 100 mg/kg hydroalcoholic L. inermis extract caused parietal bones not to develop and extra ribs to develop in mice fetuses 28 .

Perovskia abrotanoides: P. abrotanoides has several uses in Iranian traditional medicine including treatment of parasitic infections. The ethanolic extract of this plant causes certain anomalies such as spina bifida, aglossia gastroschisis, polydactyly, and tarsal extensor as well as skeletal anomalies. However, the induced maternal toxicity was not highly severe in the studied groups ²⁹.

Silymarin: Silymarin is a plant-based compound. One of the main constituents of silymarin, named milk thistle, has many uses in Iranian traditional medicine including treatment of liver diseases. In addition to inducing weight loss, this plant-based compound caused craniofacial, limb, and vertebral column malformations in mice fetus. In addition, silymarin caused growth restriction in the mice and therefore should be cautiously prescribed during pregnancy ³⁰.

HESA-A: HESA-A is a combination of aquatic plants consisting of latisulcatus (king prawn; family: Penaeidae), *Carum carvi* L. (Apiaceae), *Penaeus* (Melicertus), and *Apium graveolens* L. (Apiaceae). This plant has antitumor and cytotoxic properties. However, Moallem *et al.*, studies demonstrated that HESA-A displayed teratogenic effects at 50, 100, 200, 400, and 800 mg/kg ³¹, and 20 and 40 mu/L ³² in mouse fetus.

The plants with teratogenic effects on laboratory mice and the administered doses are shown in

TABLE 1: THE MOST IMPORTANT IRANIAN MEDICINAL PLANTS WITH TERATOGENIC EFFECTS ON LABORATORY MICE

S.no.	Name	Botanical	Part used/	Dose	Remarks
		Name	Phytochemical		
1	Silybum marianum	Khar Maryam	Silymarin	50, 100 and 200 mg/kg/day	Craniofacial malformations, abnormalities in limb and vertebral column
2	Lavandula officinalis	Ostokhodous	Essential oil	800mg/kg for 8, 9, 12, 13 days of pregnancy	Reduced the embryo weight, CRL index, length and ossification of femur and tibia and increased the
3	Perovskia abrotanoides	Barazmobl	Hydroalcoholic and aqueous extract	0.125 or 0.25 g/kg for 8-11 dayes	number of abnormal embryos Polydactyly, spina bifida, aglossia, tarsal extensor, gastroschisis, and numerous skeletal abnormalities
4	Lawsonia inermis	Henna	Hydro alcoholic extract	(0.3 ml)10 and 100 mg/kg for 7 days	Parietal bones absent in embryos and more extra ribs

Abortive plants:

Stachys lavandulifolia Vahl: Hydroalcoholic *S. lavandulifolia* extract exert effect on pituitary—gonadal axis because of containing flavonoids. In addition, this extract causes decrease in progesterone concentration and affects fetal life adversely ³³.

L. inermis: As with teratogenic effects, hydroalcoholic *L. inermis* extract caused increase

in abortion in the laboratory mice. Mean progesterone level decreased in the treated mice ³⁴. Absus n-hexane fraction (CAF). CAF is a compound derived from *Cassia absus*. Hamidi study demonstrated that phytoestrogens present in this plant, namely chaksine and beta-sitoesterol, caused hormonal disorders and missed abortions in mice ³⁵. The plants with abortive effects on laboratory mice and the administered doses are shown in **Table 2**.

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TABLE 2: THE MOST IMPORTANT IRANIAN MEDICINAL PLANTS WITH ABORTIVE EFFECTS ON LABORATORY MICE

S.no.	Name	Botanical Name	Part used/Phytochemical	Dose	Effects
1	Lawsonia	Hanna	Hydro alcoholic	1 mg/kg and	reduced the embryo weight, CRL
	inermis		extract of leaves	10 mg/kg	index, length and ossification of femur
					and tibia and increased the number of
					abnormal embryos
2	Cassia	Cheshmizeh	Seed	100, 200, and 500	Hormonal imbalance, decline in the
	absus		extract	mg/kg b.wt./day	fertility index, and an increase in the
					rate of missed abortions of fetuses
3	Stachys	Chay Koohi	Hydroalcoholic	50, 100, 150 and	changes the activity level of
	lavandulifolia		extract of shoot	200 mg/kg between	hypothalamus-pituitary gland-gonad
	Vahl			7-12th days of	axis, decreases progesterone
				pregnancy	concentration, failure in fetus survival
4	Perovskia	Barazmobl	Hydroalcoholic and	0.125 or 0.25 g/kg	Resorption, stillborn, fetal
	abrotanoides		aqueous extract of shoot	for 8-11 dayes	malformations including spina bifida,
					polydactyly, aglossia, tarsal extensor,
					numerous skeletal abnormalities and
					gastroschisis

As with chemical drugs, medicinal plants should be taken under physicians' supervision. Medicinal plants and herbal drugs produced from these plants display various properties ³⁶⁻⁴⁶; however, their

effects depending on their compounds and even the concentration of these compounds in them 47-58. Most conducted studies have not offered any specific action mechanism of causing gene

mutations. Malformations due to herbal drugs occur usually in the first trimester, because organogenesis occurs in this period ⁵⁹. In this period, estrogenic and flavonoid plant-based compounds can be considered one of the most important causes of bone changes and malformations in fetuses ⁶⁰. There is little information about the safety or unsafety of the

herbal drugs and their derivatives ⁶¹.

In addition, scant evidence exists to determine whether the side effects are caused directly by toxic effects of the drugs or the teratogenic effects are due to inappropriate use of them or associated contaminations ⁵⁹. Nutraceutical drug interaction is another factor for exacerbated toxic effects of the medicinal plants on fetus. For example, St. John's Wort alongside antidepressants cause several side effects ⁸. Besides that, the incidence of side effects due to the medicinal plants is related to their doses of use ³⁰. Some studies reported that using low doses of certain plants had no effect on laboratory mice fetuses ^{62, 63}.

However, the side effects are caused by naturebased products mainly due to two factors. First, phytoestrogens present in these plants cause changes of hormonal Although use phytoestrogens found in the plants depends on the age, health status, and other factors, they should be used cautiously during pregnancy. For example, use of soybean should be restricted during phytoestrogens pregnancy because of Phytoestrogenic compounds in plants cause decrease in the ability of uterine tubes to support fetal growth and uterine ability to support implanting in blastocyte-stage ^{64, 65}.

Another cause of medicinal plants-induced abortion is apoptosis ³⁰. Programmed cell death in mamnals' blastocytes (in both inner trophectoderm and cell mass) is partly essential for fetal evolution and progression to subsequent stages. Deviation from normal apoptosis causes early fetal death. Medicinal plants as an external agent, can cause disruption in this normal function and exacerbate the dysfunction by the present compounds ^{30,66}.

It is a misconception that medicinal plants have negligible side effects compared to their numerous benefits and consequently such plants are not used cautiously during pregnancy ¹⁹. It is therefore necessary to take into consideration the adverse effects of the medicinal plants on infertility and associated toxicities ⁶⁰. One of the limitations of the present review is that all reviewed studies were conducted on laboratory animals, and their findings could not be definitely generalized to humans ⁶⁷.

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CONCLUSION: The present review indicated that some medicinal plants or their derivatives can display teratogenic effects if used inappropriately or without physician's order, and abortive effects in the laboratory animals. Therefore, given the significance of pregnancy, it is necessary to take into account certain cautions to use them to maintain fetal and maternal health. Plants and their derivatives should not be considered harmless merely because they are natural; therefore, any medicinal plants should be used cautiously and under physician's supervision and advice.

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