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TERATOGENIC EFFECT OF HERBAL DRUGS -A REVIEW

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ABSTRACT

Aim: 1937-Sulfanilamide tragedy, 1961-Thalidomide tragedy shows the necessity for studying teratology and teratogenicity. Widespread use and positive attitude towards herbal drugs in pregnancy needs documentation about both efficacy and safety of herbal drugs. It may prevent any future tragedy by intake of herbal drugs during pregnancy.

Backgrounds: Teratogens are chemical/physical agents that can results in malformation, growth restriction, functional disorder and even death of fetus. Teratogen can cause permanent alteration in the structure and/or function of an organ during the Embryonic or fetal life. Herbal drugs are not teratogen. But improper administration during pregnancy may cause teratogenicity.

Review of Results: The name of plants showing teratogenic effects in experimental animals are named below, i.e. *Asperagus racemosus* root methanolic extract (*Satavari), Lawsonia inermis* hydroalcoholic extract (*Madayantika*), *Gloriosa superba* Linn hydroalcoholic Tuber Extract *(Langali*), *Datura metel* ethanolic leaves extract (*Dhatura), Plumbago zeylanica (Chitrak*), *Pippalyadi gutika , Vishamusti vati* & *Suddha Tankana.*

Conclusion: There are plenty of modern chemical medicines which have teratogenic effect on the fetus. But there are no such herbal drugs which have teratogenic effect in prescribed dose. Herbal drugs in optimum dose, duration and adjuvant generally do not cause teratogenic effect but in excess dose with improper mode of administration for a longer duration than therapeutically advised may cause teratogenic effect.

Clinical significance: Scientific validation of safety of their use in pregnancy is very less documented. Hence it is the need of the hour to explore and document the safety of herbal drugs in human species.

Keywords: Teratogen, Herbal drugs, Ayurveda

INTRODUCTION

Teratology: teras + logos,

It means study of the causes and effects of congenital malformations and developmental abnormalities [1].

Teratology is the study of birth defects, and its goals are (1) to describe and determine etiology, (2) to explore mechanisms involved in the production of birth defects and (3) to devise means of prevention [2]. Environmental factors, such as infectious diseases, drugs, chemicals, and radiation, have been shown to cause abnormal development by inducing chromosome abnormalities, specific gene changes, vascular changes, or mechanical disruption [3].

The term teratology is coined from modern medical science but its description is already told in Ayurveda, with reference to classification of diseases. According to *Acharya Sushruta and Vagbhata, Janmabala pravrita* diseases are very much similar to congenital birth defects as per the etio-pathology and clinical presentation.

In modern science, there are plenty of chemical medicines which have teratogenic effect on the fetus. But the mechanism of teratogenic effect is still unclear. There are also new terminology found in the science of teratology i.e. Functional and neurobehavioral teratology [4]. *Acharya Charak* also describes some behavior done by mother during pregnancy which leads to some congenital malformations in fetus [5]. Which indicates the science of teratology present in Ayurveda but the mechanism is still not clear.

The medicine of Ayurveda is mainly based on herb-mineral preparation. The efficacy of these medicines is time proven. But the safety of these medicines during pregnancy not yet proved. Generally the public perception towards herbal medicine is there are no side effects. But it is not true in real scene. Herbal drugs in excess dose with improper mode of administration for a longer duration than therapeutically advised may cause teratogenic effect.

MATERIALS AND METHODS:

Data mining was done by using Pub Med, Google Scholar, DHARA, and Ayush Portal database and *Ayurvedic* classics like *Charak Samhita*, S*usruta Samhita* and other classics also.

OBSERVATIONS AND RESULTS:

1. ***Shatavari*** *:- Asperagus racemosus,* family –Liliaceae,

This herb used as a *Rasayana* in Ayurveda and is considered as general and female reproductive tonic. But in this study teratogenic effect of *Shatavari* was found. There are 2 groups, in both the groups the animals are mixed in ratio of 1:3 male and female for mating.

Test group was ARM dose of 1000mg/kg/ day for 60 days	⇔	Control group 1% carboxymethylcellulose (CMC) in distilled water

Two sets of data collected: one was prenatal study (intrauterine) development of rat fetuses at 18 days of gestation and next was postnatal development of rat pups at 28days of their life. The observation points are C-R length (cm), Tail length (cm), Total length (cm), cord length (cm), placental weight (gm).

In postnatal data, the points of observation are pups per litter, number of pups died, appearance of hair, congenital abnormalities, opening of eyes, opening of ears (pinna), testis descent (in males). The P value was $^{a}<0.001$ as compared with control group. ARM showed teratogenic effects in rats [6]. For detail refer Table- I .

2. ***Madayantika***:- *Lawsonia inermis,* family- Lythraceae

This is an experimental study. The study was conducted with 120 female mature BALB/c mice between 8-12 wk. they were assigned to four groups,

G1- kept with no intervention,

G2 - intraperitoneally (ip) injected with saline (0.3 ml)

G3- intraperitoneally (ip) injected with 10ml *L. inermis* extract

G4 - intraperitoneally (ip) injected with 100 mg/kg of *L. inermis* extract

(For 7 days).

On the 19th day, caesarean section was performed on the mice and embryos were examined for abnormalities.

Conclusion: *L. inermis* may have teratogenicity and should be used cautiously during pregnancy [7]. For detail refer Table- I .

3. ***Langali*** :- *Gloriosa superba* Linn, Family- Lilliaceae

Gloriosa superba is a well-known ethnomedicinal plant. In higher dose or without purification, it is highly poisonous. Ingestion of all parts of the plant is extremely poisonous and can be fatal. Total thirty alkaloids present in tuber, seeds and flowers of *G. superba* Linn. The plant is rich in colchicines and its derivatives. The colchicine is mainly responsible for toxic effect [8].

This study conducted on *Biomphalaria alexandrina* to see the teratogenic potency of colchicine. In this study the colchicine given in different developing stages for different time period in different concentrations.

For ovicidal activity ,colchicines was given in concentrations between 10-30 ppm and caused death in all early embryonic stages i.e. fertilized egg, 2-cell stage, 4-cell stage, blastula stage and gastrula stage.

- Concentrations of 10 ppm - deceleration of development and death at the trochophore stage,
- 20 And 30 ppm caused - blastula and gastrula death.
- 50-200 ppm caused death among late embryonic stages (trochophore and veliger stages).

The teratogenic effect of colchicine on snail embryos at varying stages and varying doses, reported that gross congenital malformations were found in a significant number of embryos especially at trochophore stage[9].For detail refer Table- Ⅰ .

4. ***Dhatura***:- *Dhatura metel, Family- Solanaceae*

In this study twenty rats (12 females and 8 males) were taken. The females are divided into 4 groups, each group having 3 rats. The gestation period in female rats is normally about 21-23 days. So extract of *Dhatura* given in different time period of the gestation to see the effect of medicine in a constant dose. After mating with male rats the rats had gave birth averagely 6 pups in group C and D. No pups in group A and there is evidence of abortion in Group B by vaginal bleeding on gestational day 14 and 15.

4 groups are divided as below.

Group A -500 mg/kg body weight of the extract on the first day of fertilization to the end of gestation period.

Group B -500 mg/kg body weight on the 8th day of fertilization to the end of gestation period,

Group C -500 mg/kg body weight on 15th day of fertilization to the end of gestation period

Group D -normal saline throughout the gestation period

Administration of extract was stopped for Group C after delivery, for Group B after noticing the abortion and for Group A after 25 days. Two litters in each group were sacrificed on the day of parturition (day 0) and 14 days after parturition.

The lumen of the third ventricle was larger in the histological observation of group C as compared to that in group D, which suggests retarded hippocampal development. This can be as a result of retarded cell proliferation and differentiation in this part of the brain. So it has teratogenic effect in the later stage of gestation. So it should be avoided during organogenesis [10].For detail refer Table -1.

5. ***Chitrak***:- *Plumbago zeylanica, Family*-Plumbaginaceae

Chitrak is an herbal drug used abundantly as digestive and carminative. Many times they can be prescribed to a pregnant woman in day to day OPDs. But in ancient

time C*hitrak* also used as abortifacient for unwilling pregnancy. For testing the teratogenic effect of *Chitrak* the study was conducted with 8 mice. They were divided into two groups, i.e.; group B and C. They were kept with male mice overnight in a separate cage in the ratio of 1:1 respectively. The gestation period of mice is 19 days, and organogenesis period is between days 6 to days 15. Hence pregnant females are exposed to *Chitrak* as teratogen on day 11.

Group-B (4 mice)	Group-C (4 mice)
Chitrak was given orally on 11th day of gestation.	Distilled water was given as vehicle

In group B, the number of fetus is 24. There was no gross anomaly observed in both the groups [11]. For detail refer Table-I .

6. Pippalyadi Vati

Pippalyadi vati is an Ayurvedic contraceptive described in Ayurveda classics containing equal parts of powdered seeds or fruit berries of *Embelia ribes*, fruit of *Piper longum* and borax powder. In this study 2 groups

Pippalyadi Vati group (trial group)	Gum Acacia group (control group)

Pippalyadi Vati was fed orally to two groups of pregnant rats: 2.5 times to one and five times to the other than the recommended dose for humans. Result shows that: The control and the gum Acacia groups did not show such herniation. But treated group (*Pippalyadi Vati)* shows teratogenic effect in high dose than the normal human dose [12].

7. Vishamusti vati & Suddha Tankana

VismustiVati and Suddha Tankana is two commonly used medicines in Ayurveda.

Vismusti Vati- Suddha Kuchla (*Strychnos nuxvomica*), *Ras Sindur, Lavang, Loha Bhasma, Jatiphal* and *Kshudra Ela*,

Sudha Tankana - Chaukia suhaga (sudhha Tankana) and *Suddha Hingul*.

At the dose of 175mg/kg of aqueous solutions of *Visamusti Vati* shows 63.52% fertility controlled and at the dose of 300 mg/kg aqueous solutions of *Suddha Tankana* shows 33.33% fertility controlled when given orally from day 1 to day 7 of post mating period. With increasing post mating period, the antifertility activity gradually reduced and the born fetuses showed gross remarkable external morphological and skeletal defects. Each drug has 2 groups i.e.: drug treated and control group. The drugs were given orally from day 1 to day 7 of post-mating period while control groups received 1% gum Acacia. None of the fetuses of control group showed any gross visceral or skeletal defects. But VV and ST shows positive Teratological effect on newborns, hence medical termination of pregnancy, in such cases is a must [13].

8. Marijuana (<u>Bhanga</u>)

Prenatal exposure of *Bhanga* may cause delayed maturation of the visual system in infants [14].

DISCUSSION

Teratogen is an agent or factor that causes malformation in the embryo. The cause of malformation may be Toxic substances like, drugs and environmental toxins in pregnancy, Vertically transmitted infection, Lack of nutrients (lack of folic acid in pregnancy for humans can result in spina bifida), Physical restraint (Potter syndrome due to oligohydramnios in humans), Genetic disorders, Metabolic imbalance (ex- Alcohol consumption during pregnancy) [15] etc.

In *Ayurveda Acharyas* have described many things to be avoided by mother during pregnancy in terms of *Aaharas* and V*iharas* and if those avoidable things indulged by the *Garbhini (pregnant lady),* then so many abnormalities occur in progeny. Ex: Intake of *Tikshna* and *Ushna* (hot) foods in excessive quantity may leads to death of fetus, abortion, cachexia. Addiction of wine makes the offspring constantly thirsty, short of memory and fickle minded. Different abnormalities occurred by excessive intake of particular type of predominant *Rasas* of food. But there is no research work done in this area. As pregnant lady and children are vulnerable group for research, proper research work may not be possible. But experimental study can be possible.

As like these conceptual studies there is also lack of research work in the field of herbal drugs. No toxicity study and lethal dose study on each herbal plants or herbomineral medicines are available. In this review work there are few plants available in which teratogenic study found and there are also some plants present on which safety findings are found. But all these are dose and duration dependent.

The review work shows that drugs having contraceptive action (*Garbha nirodhaka prabhav*) and abortifacient action (*Garbha sravaka prabhav*) have potent teratogenic effect in experimental models. But there are no such studies reported of herbal drugs in human embryo. There are also a lot of studies of teratogenicity on other herbal drugs which shows no teratogenic effect in low doses and may cause teratogenic effect in high doses. Ex: *Ashwagandha* (*Withania somnifera*), *Punarnava* (*Boerhavia diffusa), Narangi (Citrus aurantium), Nimba (Azadirachta indica), Jatamansi (Nardostachys Jatamansi), Bala (Abutilon indicum), Yastimadhu (Glycyrrhiza glabra).*

Acharya charak also told that in *Sutra Sthana*,

A potent poison becomes the best drug on proper administration. On the contrary, the best drug too can become a potent poison if used incorrectly.

Herbal drugs with appropriate dose and duration may not cause teratogenic effect but in excess dose with improper mode of administration for a longer duration than therapeutically advised may cause teratogenic effect. Ayurveda classics also told about which work and which diets should not be done by the mother during pregnancy. So those should be followed by every pregnant lady for their better progeny.

CONCLUSION

Teratogenic study, maximum lethal dose and safe drug and doses of Herbal drugs should be carried out. Also it needs proper documentation and scientific validation of safety of their use in pregnancy. Many herbal drugs shown teratogenic effect in experimental animals but are safe to use in human and hence it is the need of the hour to explore and document the safety in human species too.

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Table 1. Herbal plants and teratogenic effects

Sl no	Name of Plants	Dose and duration	Animal	Teratogenic effect
1	*Asperagus racemosus* root Methanolic extract (***Satabari***)	1000mg/kg/body weight for 60 days	Charles foster rat pups	Prenatal study- increased resorption of foetus, gross malformation i.e. swelling in legs, IUGR with small

				placental size. Postnatal study - decreased number of pups per litter and increased mortality of pups and delayed developmental parameters
2	*Lawsonia inermis* Hydroalcoholic extract ***(Madayantika)***	100mg/kg body wt.	BALB/c mice between 8-12 wk	Parietal bone absent in 90% embryo, more extra ribs observed in G3 and G4. But more in G4. Anencephaly and exencephaly abnormalities were only observed in the G3. Skeletal abnormalities and height and weight loss in embryos.
3	*Gloriosa superba Linn* Hydroalcoholic Tuber Extract ***(Langali)***	Colchicine 1-3 ppm and 4- 5 ppm	*Biomphalaria alexandrina*	Anti-fertility activity scarcely produced abnormal embryos. Induce high percentage of abnormalities.
4	*Datura metel* ethanolic leaves extract ***(Dhatura)***	500mg/body kg wt	Rats	Group A- no implantation, Group B- abortion on the 7th day after administration, Group C- litters showing retarded hippocampus development and neural degeneration Group D- (control) normal development.
5	*Plumbago zeylanica* ***(Chitrak)***	100mg/body kg wt orally with 0.5ml of distilled water	Mice	Stunted growth, subcutaneous and deep hemorrhage, kinking of tail, protrusion of back of head.
6	***Pippalyadi gutika***	2.5 times to one and five times to the other than the recommended dose for humans	Rats	Fetus-LBW and smaller in length. Developmental defects of soft tissues and skeletons, Herniation of intestines into umbilical cord Mother-Less weight gain during gestation
7	***Vishamusti vati & Suddha Tankana***	175mg/kg of aqueous	Rats	Kinking of tail- 61.12% in 3l fetus in 'VV' treated

		solutions of *Visamusti Vati*. 300 mg/kg aqueous solutions of *Suddha Tankana*		group and 6.25% in 32 fetuses in 'ST' group, Syndactyly - 3.22% in VV and Nil in ST group. Skeletal malformation increased in VV group than ST group. Example of skeletal deformities are Cleft Palate, Non-ossification of sternum, Non-ossified Atlas Bone, Non ossification of skull bone and caudal vertebrae, Metatarsal fused in hind limb and non-ossification of ribs. Clubbing of limb found in ST group.