



### Research Article

## Safety of Siddha Herbal Antenatal Drug Bavana Panchangula Thailam established through Teratogenicity Screening in Zebra Fish Model

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### Abstract

Background: Embryonic period is the period with greatest risk for major malformation that may occur with the growing foetus. Medication or any supplements taken during the time of gestation can give risk to fetal malformation and congenital birth defect. The thalidomide tragedy which provoked the medical world to defend the motherhoods. Aim: The aim was to evaluate the Medicine *Bavana Panjangula thailam (BPT)* for teratogenicity screening which been indicated for *Karpasoodu*, meant as embryonic malformation. Hence, it is suggested for maternal groups from the first trimester to third trimester. Methods: The trial drug *Bavana Panjangula Thailam*, an oil based medicine, administered through oral route by micropipette to zebra fish with 10µl, 50 µl, 100 µl respectively and lastly control group, without medication. And embryos collected from the respective groups and inspected for any malformation in organogenesis or mortalities in zebra fish model. Result: Inverted Microscope equipped with phase contrast function, camera and software for image optimization were used to record the development of embryos for 24, 48, 72 and 96 hours. Neither malformation, nor mortalities were observed in all the groups. Conclusion: This study concludes that this *Siddha* polyherbal formulation BPT has no potency for causing any teratogenicity in the wide range of tested dose in zebra fish model.

**Keywords:** *Bavana Panjangula Thailam*, *Karpasoodu*, Micropipette, Organogenesis, *Siddha*, Teratogen, Zebra fish.

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## Introduction

The Indian system of medicine is an ancient system of medicine which have great antiquity.(1) So that it enhances the healthy living through which it improves the longevity of life.(2)

Siddhars in ancient days have adopted and followed the principles for preparing all medicines like herbals, mineral and metals for their classified diseases in different categories. They have advised to encounter the diseases initially with herbal medicine and then with mineral and metal combination of drugs. (3)

The drugs which would be given at gestation period must be subjected to teratogenicity screening. The history revealed that the

drug Thalidomide was well known teratogen that generated congenital malformations in embryo. The consequences of Thalidomide were the phocomelia and so on. The concern about medication during pregnancy and lactation was emphasized by the historical event such as thalidomide tragedy in 1960s and diethylboestrol in 1971 by US Food and Drug Administration regards drug labelling. (4) Exposure to the teratogen affects the fetus or embryo depending on the duration of exposure and amount of the teratogenic substance. It will induce malformations in foetus, which results in changes in the behavioral or emotional development of the child and decreased intellectual quotient (IQ). Additionally, teratogens also affect pregnant women and cause complications such as preterm labours, spontaneous abortions, or miscarriages. The thalidomide tragedy demonstrated the necessary for drug testing.(5)

For every stage of life, *Siddhars* have recommended medicines for the wellbeing. Most importantly during the time of gestation. Siddha science suggests some important month specific medications in trimester. (6)(7) Among the various *Siddha* formulations indicated for healthy gestation and child birth,

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Bavana Panjangula Thailam is quite promising medicine in the experience of many traditional Siddha medical practitioners. The formulation is stated in Theraiyar Thaila Varga Surukkam treatise by Sage Theraiyar.(8)

Siddha herbal formulation BPT containing Aamanaku vithai (Castor seeds – Ricinus communis), Sevvilaneer (Red variety of Cocos nucifera) and Katralai (Aloe barbadensis). This Siddha herbal formulation is being widely used for common pregnancy symptoms such as urinary tract infection, dry skin, constipation that have been classified under Karpasoodu.(8)(9)

In Siddha literature BPT is recommended to be given from the first trimester through the end of the third trimester. The recommended dose range of ¼ to 1/8 palm (8.74 - 4.37 gm).(8) But the apprehensions in the scientific community about effect of drugs on the embryo forestalls the administration of such drugs during gestation. Therefore, in order to get over such ill-founded apprehensions, the drugs are to be subjected to teratogenicity screening. The test drug BPT though indicated in Siddha literature for antenatal administration, it needs to be validated for safety during pregnancy.

### Literature review

The trial drug BPT was prepared traditionally as described in Theriyar Thaila Varga Surukkam indicated for Karpasoodu.(10) The constituents of Bavana Panjangula Thailam are Ricinus Communis (Aamanaku vithai), Cocos nucifera (Sevvilaneer), Aloe barbadensis (Sottru Katralai) and the taxonomical classification had given in the table. (Table 1).

**Table 1. Taxonomical Classification of Plant**

	Aamanaku vithai ( <i>Ricinus communis</i> )	Sottru Katralai ( <i>Aloe barbadensis</i> )	Sevvilaneer ( <i>Cocos nucifera</i> )
Domain	Eukaryota	Eukaryota	Eukaryota
Kingdom	Plantae	Plantae	Plantae
Phylum	Spermatophyta	Spermatophyta	Spermatophyta
Subphylum	Angiospermae	Angiospermae	Angiospermae
Class	Dicotyledonae	Monocotyledonae	Monocotyledonae
Order	Euphorbiales	Liliales	Arecales
Family	Euphorbiaceae	Aloaceae	Areaceae
Genus	Ricinus	Aloe	Cocos
Species	R. Communis	A. barbadensis	C. nucifera

### Ricinus Communis (Aamanaku Vithai)

The seed contains 45% of fixed oil which consists of glycosides of ricinoleic, stearic and dihydroxy stearic acids and lipases and a crystalline alkaloid ricinine. It has laxative, emollient, anti-asthmatic, hepato-protective, lipolytic activity. It is believed that ricinoleic acid acts as an anionic surfactant that reduces net absorption of fluid and electrolytes and stimulates intestinal peristalsis.(11)

### Aloe Barbadensis (Sottru katralai)

Aloe gel contains 99 % of water and consists of brady kininase, magnesium lactate, anti- prostaglandin compounds. It has an action of Anti-inflammatory, anti-fungal and wound healing effects. Emollient, Anti-inflammatory and anti-microbial.(12)

### Cocos Nucifera (Sevvila Neer)

Coconut water contains 95.5% of water, sugars, fat (0.02%), calcium, Phosphorus, mineral salts, iron, B complex vitamins and Folic acid. It has Refrigerant, demulcent, and mild diuretic action.

Coconut water has long been known for its therapeutic effect on the urinary and reproductive system. During the second world war coconut water was used as a short term intravenous hydration and resuscitation fluid. In Ayurvedic medicine, tender coconut is said to have the following properties such as “unctuousness, sweetness, increasing semen, promoting digestion and cleaning the urinary tract path. Traditionally prescribed for dysuria, gastritis, burning pain in eyes and indigestion. (13)

## Methodology

### Trial Drug preparation

The boiled rice was mixed with water and allowed to stand overnight. The very next day it was filtered and the liquid was collected. As per literature this fluid is mentioned as Neeragaram. The seeds of Ricinus communis was crushed and soaked in Neeragaram and kept for one day. Next day it was filtered and kept aside. Like the seeds of Ricinus the aloe vera also crushed and soaked in Neeragaram (fermented rice water) and kept for one day and filtered. The red tender coconut water was collected in a vessel and the purified Aloe vera gel and castor (Ricinus communis) seeds were added in it and boiled. Heating was continued until the oil exuded from the mixture and floats. Oil thus prepared is stored in an air tight container. (8)

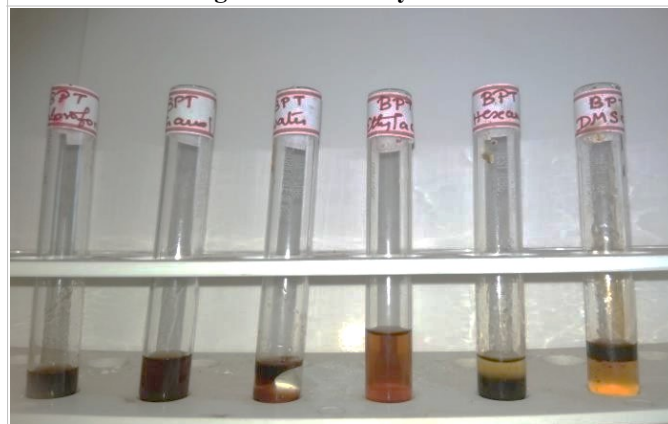
### Organoleptic properties

The test drug BPT is an oil in nature, highly viscous, dark brown, with a characteristic Odour of oil. Solvents were used in Bavana Panjangula Thailam to determine the nature of Solubility.(14) (Table 2) & (Figure 1)

**Table 2: Solubility assay Solvents used**

S.No	Solvent Used	Solubility/Dispersibility
1	Chloroform	Soluble
2	Ethanol	Soluble
3	Water	Insoluble
4	Ethyl acetate	Soluble
5	Hexane	Soluble
6	Di Methyl Sulf Oxide	Insoluble

**Figure 1: Solubility of BPT**



Solubility of Bavana Panjangula Thailam in various solvents

**Study Place:** This study was conducted at Noble Research Solutions, Chennai (Project ID:NRS/AS/0392/2019).

**Ethical approval:** This study was ethically approved by the Institutional Ethics Committee of National Institute of Siddha

(Date and IEC approval and its Number: 22-02-2019; NIS/IEC/2019/M-33)

**Study Design:** Preclinical Analytical study

**Study Sample:** Female fishes were divided into four groups (one control and three treatment groups) of six fish each group the dose of 10  $\mu$ L, 50  $\mu$ L and 100  $\mu$ L. In each group 30 embryos were collected for analysis.

**Unique features of Zebrafish:** Zebrafish share significant genetic similarities with humans, underscoring its relevance of chemical's toxicity evaluation and safety assessments aimed at predicting mammalian outcomes. Zebrafish exhibit high fecundity, producing hundreds of embryos in one spawning event from a single pair, develop rapidly to free-swimming larvae at 5 days post fertilisation (120 hpf), significantly reducing the use of experimental animals and allowing for short experimental durations. Importantly, zebrafish embryos serve as a whole-organism model that mimics the complexity of embryonic development while overcoming the limitations of *in vitro* methods. The transparency of zebrafish embryos allows the entire developmental process to be easily observed using microscopic technologies. (28)

**Dosing of test drug and collection of Embryos:** Human dosage mentioned as per *Theraiyar Thaila Varga Surukkam*, recommended morning ¼ palam (8.74 gm) & bed time- 1/8 palam (4.37gm). Human Dose was converted to Animal Equivalent dose as per the guidelines of (OECD) 236. (17) Female fishes were divided into four groups (one control and three treatment group) of six fish each group. Drug BPT administered at the dose of 10  $\mu$ L, 50  $\mu$ L and 100  $\mu$ L through oral administration for the period of one week followed by which the fish are allowed to breed with healthy male zebra fish to collect the embryos for the present investigation. Fertilized embryos are subjected to the surface sanitation and were transferred into culture plates (30 embryos/plate/ Dose concentration) (10). Exposure involved semi-static renewal condition, 25°C $\pm$  1°C and 14 light: 10 dark cycle period. Embryo development was monitored 24-hour interval for 96 hours post fertilisation (hpf). (17)

**Embryo stock:** Sterilized E3 Medium was utilized for maintenance of live embryos. 8 ml of the sterilized medium dissolve to liter to get 1X stock with inclusion of 100 $\mu$ L of 1% methylene blue used as fungicide. (17)

E3 medium contains (for Zebra fish embryos)

- 34.8 gram of NaCl
- 1.6 gram of KCL
- 5.8 gram of CaCl<sub>2</sub>.2H<sub>2</sub>O
- 9.78-gram MgCl<sub>2</sub> 6H<sub>2</sub>O

**Test condition:** Semi static renewal test. Everyday fresh medium was added to the plates containing embryo. (E.g. every24hours). (17)

**Semi static renewal test:** Semi static renewal test is a test with regular renewal of the test solution after defined periods.

E.g. Every 24hours. (17)

## Results

As per the Fish Embryo Toxicity study the embryos were observed. The inverted microscope with phase contrast function, camera, and software for image optimization. The Parameters

were observed for every 24 hours up to 96 hours. Embryo Toxicity Study Observed Parameters in zebra fish embryos (Table.3).

**Table 3: Embryo Toxicity Study- Observed Parameters in zebra fish embryos**

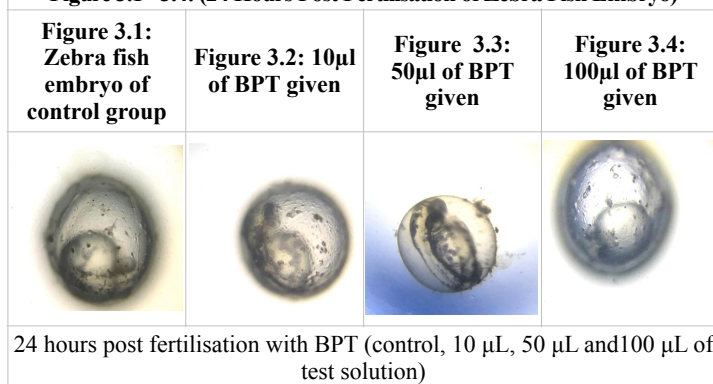
S.No	Parameters observed	Volume administered			
		Control	10 $\mu$ l	50 $\mu$ l	100 $\mu$ l
1	Developmental abnormality	NO	NO	NO	NO
2	Loss of Equilibrium	NO	NO	NO	NO
3	Pigmentation	N	N	N	N
4	Abdominal distention	No	No	No	No
5	Migration of melanophores from neural crest	AN	AN	AN	AN
6	Puffy (Swollen appearance)	NSA	NSA	NSA	NSA
7	Bent tails/Body axis	NO	NO	NO	NO
8	Pericardial edema	NSA	NSA	NSA	NSA
9	Peritoneal edema	NSA	NSA	NSA	NSA
10	Percentage survival	100%	100%	100%	100%
11	Hatching rate	100%	100%	100%	100%
12	Heartbeat	N	N	N	N
13	Yolk sac edema	NSA	NSA	NSA	NSA
14	Hyperpigmentation	NO	NO	NO	NO
15	Pectoral fin malformation	NO	NO	NO	NO
16	Trunk axis	AN	AN	AN	AN
17	Spontaneous Movement	N	N	N	N
18	Heart formation	N	N	N	N
19	Curved of Bent axis	NO	NO	NO	NO
20	Eye malformation	NO	NO	NO	NO
21	Blood circulation	N	N	N	N
22	Mortality	0%	0%	0%	0%
23	Arrested Growth	NO	NO	NO	NO
24	Craniofacial malformation	NO	NO	NO	NO
25	Peripheral ischemia and disruption of erythropoiesis	NO	NO	NO	NO
26	Accumulation of fluid around heart	NO	NO	NO	NO
27	Response to stimuli	N	N	N	N
28	Coagulation of eggs	NO	NO	NO	NO
29	Tail detachment	NO	NO	NO	NO

As in the Table 3. The Abbreviation are NO-represents None Observed, N-Represents Normal, AN-Represents Appears Normal and NSA- Represents No such Abnormality observed

**Table 4: Statistical analyses of Embryo Movement and Heartbeat (N=30)**

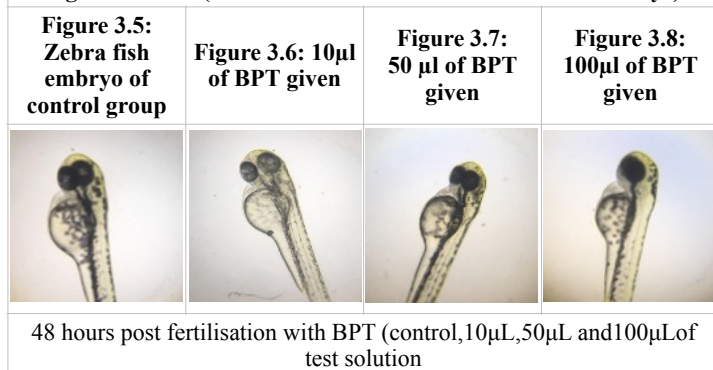
Parameters	Concentration			
	Control	10µl	50µl	100µl
Embryo Movement at 24HPF				
Mean	7.733	8.667	8.433	9.1
Std. Deviation	1.701	2.187	1.906	1.863
Std. Error	0.3105	0.3992	0.3408	0.3402
Heart Beats/Min 48 HPF				
Mean	123.6	125	123.1	127.6
Std. Deviation	2.66	3.034	3.571	5.354
Std. Error	0.4857	0.5539	0.652	0.9774

**Figure 3.1 - 3.4: (24 Hours Post Fertilisation of Zebra Fish Embryo)**



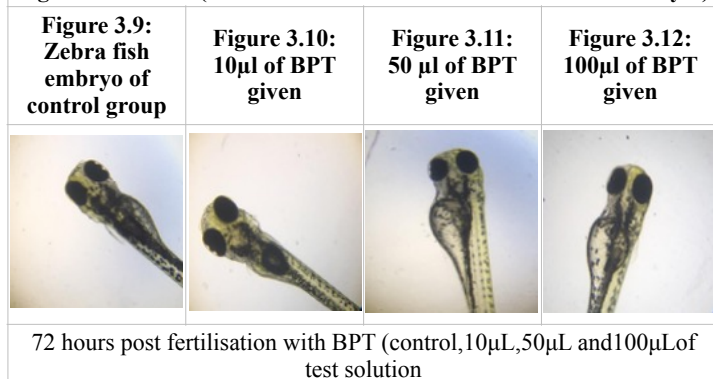
Up to 24 hours embryo of Zebra fish undergone Zygote period, Cleavage period, Blastula period, Gastrula period, Segmentation period, and Pharyngula period.

**Figure 3.5 to 3.8:(48 Hours Post Fertilisation of Zebra Fish Embryo)**

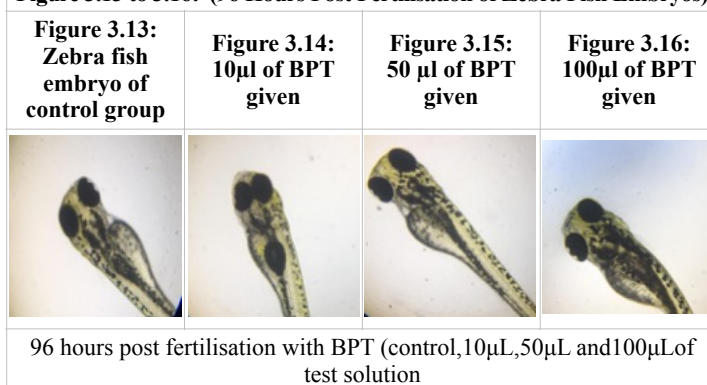


From 24- 48 hours post fertilisation Pharyngula Period to Hatching period. This period Phylotypic –stage embryo, body axis straightens from its early curvature about the yolk sac, circulation, pigmentation, and fins begin development.

**Figure 3.9 to 3.12: (72 Hours Post Fertilisation of Zebra Fish Embryos)**



**Figure 3.13 to 3.16: (96 Hours Post Fertilisation of Zebra Fish Embryos)**



96 hours post fertilisation with BPT (control, 10µL, 50µL and 100µL of test solution).

From the hour of 72 to 96-hour post fertilisation is an Early larvae period. In this period swim bladder inflates, food seeking and active avoidance behaviour appears.

(Figure 3.1 to 3.4) shows 24 hpf of zebra fish embryo. (Figure 3.5 to 3.8) shows 48 hpf of zebra fish embryo. (Figure 3.9 to 3.12) shows 72 hpf of zebra fish embryo. (Figure 3.13 to 3.16) shows 96 hpf of zebra fish embryos.

## Discussion

*Bavana Panjangula Thailam* that featured in Theriyar Thaila Varga Surukkam indicated for *Karpasoodu* mean by disease during gestation period.(18) Any drug which is administered during pregnancy should be screened for its potency to cause teratogenic effects.(19) The safety concerns during the gestational period, though it is been indicated for period of pregnancy, consumption of the drug BPT may scare the community during pregnancy as because of Thalidomide tragedy and its birth defects. (20)(21). Hence, the test drug Bavana Panjangula Thailam subjected to the test for teratogenicity. The zebra fish embryo toxicity model was chosen for the study as the fish has nearly 70% resemblance to the human genome and even more counterparts with human disease genes. (22)

In this present study, four groups each containing six fish with distinctive drug doses of 10 µl, 50 µl, 100 µl. Embryo movement was observed in the study, as zebra fish had a higher propensity for locomotion, (23) which is indicative of their brain and spinal cord being intact as and so the neuromuscular activity. A drug or chemical with teratogenic potential would affect neuromuscular function and therefore the locomotion.(24)

The observed parameters are Developmental abnormality, loss of equilibrium, Pigmentation, Abdominal distention, migration of melanophore from neural crest, puffiness (swollen appearance), bent tails or bent body axis, pericardial edema, peritoneal edema, survival rate of the zebra fish embryos in various groups, hatching rate of eggs, heartbeat, yolk sac edema, hyperpigmentation in embryos, pectoral fin malformation, trunk axis, spontaneous movements in the embryos, formation of heart, bent axis curvature, eye malformation, blood circulation in the zebra fish, mortality rate, arrested growth in growing embryo, craniofacial malformation, peripheral ischemia and disruption in the erythropoiesis, fluid accumulation around the heart, response to stimuli, egg coagulation and tail detachment. No changes were observed in all the groups (control and test groups). (25)(26)(27)

It is observed in this current study that the mean value for embryo movement in control group is 7.733. The mean value for embryo movement in dosage of 10 $\mu$ l is 8.667. The mean value for embryo movement in the dosage of 50  $\mu$ l is 8.433. The mean value for embryo movement in the dosage of 100  $\mu$ l is 9.1. Standard deviation for embryo movement on 24 hpf is 1.701 in control group is, 2.187 in 10 $\mu$ l, 1.906 in 50 $\mu$ l, 1.863 in 100 $\mu$ l. It is interpreted that Standard deviation are close to mean value. Standard error for embryo movement at 24 hpf is 0.3105 in control group is, 0.3992 in 10 $\mu$ l, 0.3408 in 50 $\mu$ l, 0.3402 in 100 $\mu$ l.

Heart Beats/Minutes on 48 hpf was observed and mean value is 123.6 in control group, 125 in 10 $\mu$ l, 123.1 in 50  $\mu$ l, 127.6 in 100 $\mu$ l. The mean value is close to each groups shows no distinctive. Standard deviation for heart rate/mins on 48 hpf were observed, 2.66 in control group, 3.034 in 10  $\mu$ l, 3.571 in 50  $\mu$ l, 5.354 in 100  $\mu$ l. It is interpreted that standard deviation are close to mean value. Standard error for heartbeat/mins on 48 hpf were observed, 0.4857 in control group, 0.5539 in 10 $\mu$ l, 0.652 in 50 $\mu$ l, 0.9774 in 100 $\mu$ l. It is interpreted that standard error are close to the 0 value shows not significant difference were seen in all groups of zebra fish embryos.

This present study shows that there is no significant abnormality noted in the considerable dosage ranges from 10 $\mu$ l, 50 $\mu$ l, 100 $\mu$ l of the test drug *Bavana Panjangula Thailam*.

## Conclusion

Siddha poly herbal formulation *Bavana Panjangula Thailam* does not have the potential to cause teratogenicity in the doses tested in zebra fish model. Since the tested doses were arrived from human dose as mentioned in the literature, this study extrapolates the safety in human doses.

## Abbreviation:

1. BPT: *Bavana Panjangula Thailam*
2. OECD: Organization for Economic Cooperation and Development.
3. hpf: hours post fertilisation

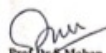
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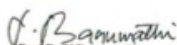
F.No.: NIS/6-20/IEC/18-19      Date: 28<sup>th</sup> Feb 2019

**CERTIFICATE**

Address of Ethics Committee: National Institute of Siddha, Tambaram Sanatorium, Chennai-600047, Tamil Nadu, India	
Principal Investigator: Dr.S.Aruldevi, 1 year, Department of Noi Naadal	
Protocol title: Safety of Bavana Panjangula Thailam usage in pregnancy determined through zebra fish model	
Documents filed	1) Protocol 2) Data Collection forms
Clinical Study Protocol - Minor Project - Part of 1 year PG study	Preclinical Study
Any other documents	-
Date of IEC approval & its number	22-02-2019;NIS/IEC/2019/04-33

  
 Prof. Dr. K. Mohan  
 Chairman



  
 Prof. Dr. V. Banumathi  
 Member Secretary

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