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Current Status of Plants Investigated for Fertility Regulation in India*

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The leads available on contraceptive remedies in ancient medicinal texts, unlike several other areas of research on traditional remedies, are rather limited. This has been partly due to the fact that limitation of family size was not a major problem at that time. One does find mention of certain emmanogogues in old texts. Some aborginal and nomadic tribes in India are supposed to use certain plant products as contraceptives but here again little authenticated information is available. Morever, according to the ancient concepts ovulation was supposed to accompany menstruation and the systemic contraceptives are recommended to be administered during that period. Some local contraceptives are also mentioned in old Ayurvedic treatises.

Table I. Type of fertility regulation activity tested in Indian plants.

Female	Male
Antiovulatory	Spermicidal
Anti-implantation	Antispermatogenic
Abortifacient (early/late)	Inhibition of fertility
Oxytocic	
Inhibition of fertility	

Documented clinical data in most of them are, however, lacking.

There have been sporadic attempts for over 50 years to obtain uterotonic or interceptive substances from plant sources but a real integrated programme has been only of a recent origin. The first such programme was initiated

Table II. Indian plants with abortifacient activity.

Plant	Part used	Active constituent	Reference
Abroma augusta (L.)Willd.	Root		41
Achyranthes aspera Linn.	Bark		41, 42
Adhatoda vasica nees	Plant	Vasicine	2
Ananas comosus(L.) Merr.	Leaf		7, 40
Aristolochia indica Linn.	Root	Aristolic acid	44, 45, 48
		p-coumaric acid	46, 47
Carica papaya Linn.	Fruit		24
Cichorium intybis Linn.	Plant		57
Plumbago zeylanica Linn.	Plant	Plumbagin	59
Woodfordia fruiticosa (L.) Kurz.	Flower		41

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at our Institute and some other CSIR Laboratories have also been involved since. In addition, the Indian Council of Medical Research and the Central Council of Research in Indian Medicine have been funding work on medicinal plants for nearly two decades for this purpose.

The various types of activity that have been investigated in the country have been presented in Table I. A wide variety of animal models have been used but a few investigators have tried to obtain botanically authenticated samples of plants. This has led to a lot of variability in data from different laboratories and sometimes from the same laboratory. The plants evaluated at the Central Drug Research Institute, Lucknow (CDRI), however, contain this data and their herbaria sheets are always prepared and preserved. A brief review of the positive results of Indian investigators is presented first and is followed by the work conducted at our Institute.

1. Abortifacient/uterine stimulant plants: Table II shows 9 plants whose extracts/pure costituents have been shown to possess abortifacient properties in rats or mice. Nine plant extracts/isolated compounds with good uterine stimulant activity are given in Table III and these have generally been tested on gravid or nongravid rodent uterine strips *in vitro*. In some cases, however, human myometrial strips and *in vivo* methods have been used. Vasicine from *Adhatoda vasica* is the only material that induced abortion in mid and late pregnancy in different animals and has reached clinical trials[2]. Aristolic acid and *p*-coumaric acid isolated from roots of *Aristolochia indica* have also shown promising abortifacient (early) activity in mice and are under development[44~48].

Table III. Indian plants with good uterine stimulant activity.

Plant	Part	Active constituent	Reference
Abrus precatorius Linn.	Seed		62
Adhatoda vasica Nees*	Plant	Vasicine	2
Aloe barbadensis Mill.	Leaf		62
Annona squamosa Linn.	Seed		62
Carica papaya Linn.	Fruit latex		62
Curculigo orchioides Gaertn	Rhizome	Flavone glycoside	68
Euphorbia dracunculoides Lamk.*	Plant		58
Plumbago zeylanica Linn.	Plant	Plumbagin	8
Sida rhombifolia Linn.	Plant	Alkaloid	39

* Active in several species including human myometrium.

2. Anti-implantation activity: Over 100 plants and fractions or compounds from 22 plants have been investigated in the country in 1~5 or 1~7 days *post-coital* schedule in rats or mice. Of these, extracts/pure constituents of 25 plants showed 60% or more activity (Table IV). Only one of them, Ensete superbum was active in hamsters[16]. The constituents of *Aristolochia indica* have been studied in somewhat greater detail, though most of the data has been generated in mice[43~47,50~53]. Unfortunately oral administration of methylester of aristolic acid for 30 days produced liver and kidney damage[54]. We have been unable to confirm the activity of *p*-coumaric acid in other rodents.[73] The most promising lead, however, appears to be a constituent of seeds of Ensete superbum "VIDR-2GD" which showed anti-implantation activity in various rodents including hamster[16]. The

Table IV. Indian plants with anti-implantation activity.

Plant	Part	Reference
Abroma augusta(L.) Willd	Root	41
Abrus precatorius Linn.	Seed	13
Achyranthes aspera Linn.+	Bark	41
Aristolochia indica Linn.+*	Root	43-47, 50-53
Artemisia scoparia Wald ST.*	Plant	10
Butea monosperma(Lamk.) Taub.	Seed	23, 30
Carica papaya Linn.	Unripe fruit	21, 24
Crotalaria juncea Linn.	Plant, Seed	60, 61
Cuminum cyminum Linn.	Seed	20
Curcuma longa Linn.	Rhizome	19, 23
Daucus carota Linn.	Seed	23, 56, 67
Embelia ribes Burm F.*	Berries, Root	1, 23
*Ensete superbum***	Seed	16
Hibiscus rosa-sinensis Linn.*	Flower	6, 26, 34, 36, 37
Hyptis suaveolens (L.) Poit	Leaf	20
Lygodium flexosum	Plant	17
Mentha arvensis Linn.	Leaf	9, 23
Ocimum sanctum Linn.	Leaf	6, 70
Plumbago zeylanica Linn.	Root, Fruit	26
Polygonum hydropiper Linn.*	Root	22, 23, 57, 70
Pueraria tuberosa DC	Root	11, 66
Randia dumetorum Lamk.*	Seed	55
Sapindus trifoliatus Linn.	Seed	23
Tabernaemontana heyneana Wall.*	Root	38

+ Active in mice; *Active constituent isolated; ** Active in hamster

difficulty in obtaining adequate quantities of seeds of this wildly growing plant has, however, limited further developmental studies on this compound. *Metaxylohydroquinone* isolated from *Pisum sativum* seeds generated considerable interest in fifties. The animal data on this material is rather contradictory; in contraceptive trials its failure rate was almost 50% and there is little interest now in this once exciting compound[4,5,63,64].

3. Other types of activity in the female: Plants listed in Table V have been investigated for anti-ovulatory activity as well as for inhibition of fertility in the female animals using a wide variety of schedules. However, the results did not encourage further pursuit. Morever, in view of availability of potent synthetic anti-ovulatory agents the utility of these approaches appears rather limited.

4. Investigations in the male: A limited number of plants have been investigated for antispermatogenic activity in the male but all the active plants interferred with both gametogenic and endocrine functions and are hence not suitable for further development[15,18,27,31~33,48]. Few plants have been reported to reduce fertility in male mice or rats without affecting spermatogenesis and need further pursuit[12,14,49],

Table V. Other promising Indian plants active in female.

Antiovulatory			Inhibiting fertility		
Plant	Part	Reference	Plant	Part	Reference
Albizzia lebbeck(L.) Willd.*	Seed	71	*Mallotus philippinensis* (Lamk.) Muel Arg	Hairs of capsule	25
Aloe barbadensis Mill.	Leaf	26	*Piper betle* Linn.	Leaf	69
Mentha arvensis Linn.	Leaf	29	*Podocarpus brevifolius* Stapf.	Leaf	35
Polygonum hydropiper Linn.	Root	29	*Punica granatum* Linn.	Fruit	35
Vitex negundo Linn.	Plant	72	*Sida acuta* Burn F.	Plant	35

* Active saponins have been isolated.

Table VI. General plan of work on medicinal plants at CDRI.

1. Collection and botanical authentication of plant material
2. Preparation of herbarium sheet and herbarium specimen
3. Preparation of 50% ethanol extract
4. Biological screening
5. Fractionation of active extracts
6. Confirmation of activity in the fraction
7. Isolation and characterisation of active constituent (s)
8. Detailed biological and toxicological evaluation of active constituent(s)
9. Clinical studies

Table VII. Types of biological activity of medicinal plants investigated at CDRI.

I. Chemotherapeutic

1. Antiviral	2. Antifungal
3. Antibacterial	4. Anticancer
5. Anthelmintic	6. Antiprotozoal

II. Endocrinal

1. Antifertility	2. Hypoglycemic

III. Other pharmacological

1. Cardiovascular effects	2. C.N.S. effects
3. Spasmolytic	4. Diuretic
5. Anti-inflammatory	6. Hypolipedemic

Some plants have also been tested for spermicidal activity but no promising leads were detected[3].

5. Plants tested for fertility regulation at CDRI: Testing of plants for antifertility activity is an important part of a broad based programme of screening natural products for biological activity at CDRI. Table VI presents the general plan of work and Table VII indicates the total spectrum of the screening programme. The test systems currently employed for primary screening of fertility regulating plants are shown in Table VIII. A summary of our results is shown in Table IX[73]. We have thus several plants identified for further developmental work.

Our work on isolation of semen coagulating and spermicidal agents from plant sources has been quite rewarding. Twenty plants showed good semen coagulating activity[28] and 8 plants had promising spermicidal activity[65]. We feel that a combination of a semen coagulant with a spermicidal agent should provide an ideal local contraceptive. In the meanwhile we have completed developmental work and Phase I clinical studies with total saponins of *Sapindus mukorosii*. The total saponins from the fruits of this plant were as active as Nonyl-9.

In conclusion it is evident that the major effort in India has been directed to identify plants with interceptive activity. A few promising leads have been obtained but most of them have not yet been adequately followed and very

Table VIII. CDRI test systems for screening fertility regulating plants.

Activity	Species	Schedule
Uterine stimulant	Rat	DES primed uterus-in vitro
Anti-implantation	Rat	Days 1-7 p.c.
	Hamster	Days 1-8 p.c.
Abortifacient	Rat	Days 12-14 p.c.
Spermicidal	Rat	Vasal or cauda epididymis sperm—in vitro
	Human	Liquified semen—in vitro
Semen coagulant	Human	Fresh semen—in vitro
Antispermatogenic/functional sterility	Rat	Days 1-60, fertility testing at 2, 4 and 8 weeks

Table IX. Indian plants tested for fertility regulation at CDRI.

Activity	Number tested	Number showing over 60% activity	Number promising	Number under development
Uterine stimulant	450	16	2	2
Anti-implantation	340	*1+4	2	2
Abortifacient	296	**1+19***	1	1
Spermicidal	2000	16	8	1
Semen coagulant	2000	49	20	2

* in rat only, ** early, *** late.

often data have been generated in small group of animals only. Several groups in the country are, however, now aware of the need of use of properly authenticated plant samples, standard methods of extraction and the need of proper experimental schedules to get reproducible results. The prospects of some of these reaching clinical evaluation during the next 4-5 years appear good.

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* These reports include proper botanical authentication of plants used.