

A review of antifertility folkloric plants tested in laboratory animals

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RESUMO: O uso de princípios naturais como terapia alternativa, em países onde grande porcentagem da população não tem acesso à assistência médica, é muito difundido. Esses princípios naturais são usados como alimento ou remédio e, até mesmo, como agentes contraceptivos. É necessário estabelecer uma relação entre os costumes populares e as informações atuais sobre a origem das substâncias antifertilidade, e conhecer seus mecanismos de ação. Os agentes antifertilidade podem atuar em muitas áreas como hipotálamo, hipófise, ovário, oviduto, útero (incluindo endométrio, miométrio e cérvix) e vagina, interferindo na síntese e liberação de hormônios (folículo-estimulante, luteinizante, esteróides), na ovulação, no transporte da célula ovo e no processo de implantação. O objetivo deste trabalho é chamar a atenção para o amplo uso de plantas, popularmente usadas como abortivas, e verificar se o efeito dessas plantas é compatível ao encontrado nos animais de laboratório. Para isso foi realizada uma revisão de literatura, incluindo diversas plantas popularmente utilizadas como abortivas, as quais foram testadas em animais de laboratório para confirmar seu efeito.

Palavras-chave: Plantas medicinais, comportamento contraceptivo, hormônios, animais de laboratório.

ABSTRACT: A review of anti-fertility native folklore plants in laboratory animals. The use of natural active principals is widespread among a great proportion of the rural population, or by people who do not have easy access to medical assistance. These active principles are used as food or medicines, and even for purposes of contraception. It becomes necessary to establish a relationship between the folklore habits and current information on the nature of anti-fertility substances, and knowledge of their mechanisms. Anti-fertility agents may exert their actions in a number of areas, (hypothalamus, anterior pituitary, oviduct, uterus, and vagina), inhibiting synthesis and/or liberation of hormones (follicle-stimulating, luteinizing, and steroid hormones), ovulation, ovum transportation, and implantation process. Therefore, a review of literature was carried out, including of several plants used by women as abortifacient and anti-fertility agents to compare their effects with those obtained among laboratory animals.

Key-words: Medicinal herbs, plant, fertility, anti-fertility, hormones, animals

INTRODUCTION

The population explosion is posing an alarming concern all around the world, even threatening the survival of mankind. How to control the birth rate is a problem which has drawn the attention of political leaders and governments and also scientists; not only from the highly populated developing countries but also from many industrialized countries. Population of countries which support the family planning needs new and effective contraceptive agents and/ or methods that have a minimum of side reactions, providing a maximum protective effect (Sethi *et al.*, 1991). The use of natural principles as an alternative therapy, in countries where a large percentage of the population does not have access to medical assistance, is widespread (Di Stasi *et al.*, 1989).

The plant extracts are traditionally used by

the majority of the disadvantaged population, living mainly in the countryside, or by the people who leave the countryside to live on the city. In order to establish the relationship between the folk habits and current information on the nature of anti-fertility substances and the way they act, it is necessary to: identify botanically the species used; search the literature for the already known chemical components of these species, or to characterize them, in this work; to try to discover the pharmacological basis that could justify the empirical use of those plants (Weniger, 1982). Nevertheless, there is little information about the toxic effects of many of these plants that are frequently used in the cure of diseases, but it is extremely important to know the effect of these plant extracts. It is of importance that there be an exact botanical classification of the plants for pharmacological research, since insignificant mistakes in this matter can lead to the study of

similar plants with different chemical components (Ramos *et al.*, 1992).

Almost every pharmacological category of drugs has, as prototype, a substance of natural origin; thus it is reasonable to believe that the plant kingdom should yield an effective anti-fertility drug. The problem underlying the search for natural anti-fertility drugs, basically concerns the choice of species of higher plants that should be examined in an animal system for their potential anti-fertility effects. There appears to be only three paths to follow, i. e., 1) test plants that have folkloric reputation of being used by women as oral contraceptives, 2) test plants that are known to contain components that theoretically could affect the female cycle to produce anti-fertility effects, or that contract the uterus potentially, and 3) make a random collection-mass screening of all available plants for anti-fertility effects. The first two of these methods appear to be the most practical and realistic ones (Farnsworth *et al.*, 1975). The present report is a review of published literature on the anti-fertility activity of Brazilian medicinal plants. Several plants have been examined for anti-fertility activity. Many of them showed a positive activity while some did not show any. Thus, the purpose of this review is to draw attention to the large use of plants, popularly used as abortive, and to verify if the employment of these plants is in agreement with tests made with laboratory animals.

Anti-fertility Mechanisms

The World Health Organization has set up a Task Force on plants for fertility regulation, the strategic plan of which is to identify novel drug prototypes found in plants which have been alleged to have fertility regulating properties (Sethi *et al.*, 1991).

Anti-fertility agents that prevent ovulation and/or fertilization are commonly referred to as contraceptive agents, whereas those that act after implantation have been called abortifacients. The term interceptive has been used by some workers to refer to compounds that act after the occurrence of fertilization, but prevent the embryonic implantation process (Morris & Wagenen, 1973). Most of the plants are used in cases of presumed pregnancy. But it is difficult or impossible to distinguish between their contraceptive or abortive properties, since their more or less regular use may change the duration of the menstrual cycle and nothing enables one to determine if the patient is pregnant or is experiencing a simple delay of menses. Some plants species are used in cases of recent pregnancy, as well as in cases of advanced pregnancy, up to third or fourth month (Weniger, 1982).

Although the physiological and pharmacological mechanisms are important for implantation process, we should consider others

factors involved during an investigation using plants like: sensibility of the animals, dose of herb extract used, period and route of administration of the extract given to the animals (Nishimura & Tanimura, 1976). According to Claeson *et al.* (2000), vasicine, a chemical component of the *Adhatoda vasica*, administered intraperitoneally (2.5, 5 and 10 mg/kg body weight) in rabbits caused abortifacient activity after parenteral administration, while no activity was observed after oral administration. This experiment showed that different routes of administration presented different results. Claeson *et al.* (2000) also verified that hamsters that intraperitoneally received 5 mg of vasicine/kg body weight, after day 7 of pregnancy, presented a failure pregnancy or abortifacient activity, but the rats given the vasicine in same dose and period of administration showed no anti-implantation effect. Thus, the difference of sensibility of the animals is very important for an investigation, as verified in the paper cited.

In general, there are a great many abortifacient plants and the chemical structure of their active principles varies widely. Therefore, there also must be several action mechanisms. There is a number of areas within the female mammalians organs where substances that have anti-fertility effects may exert their action(s); these areas are the hypothalamus, anterior pituitary, ovary, oviduct, uterus (including the endometrium, myometrium, and cervix), and vagina. A given compound may exert its anti-fertility effects in more than one of these areas and not necessarily by the same pharmacological mechanism. Conversely, different compounds may act in the same area to inhibit fertility but in some cases by different mechanisms (Farnsworth *et al.*, 1975).

A review of literature was carried out and it included several plants having folkloric reputation as abortive and anti-fertility agents. The search of the literature extends though 2001. The sources of references included Biological abstracts, Pubmed, Lilacs, and books of herbal and/or medicinal plants. It was intended to list the folkloric medicinal plants used by women as contraceptives or for anti-fertility activities, and to correlate the effects of these plants in laboratory animals. The Table I presents the names of these plants, whose substances were under tests for crude extracts and were injected in vivo, by different administration route, without control of specific topic effects.

In this section, we cited some areas within the female mammal where the plants having anti-fertility effects may exert their action.

Pituitary gland-hypothalamus

The hypophysis secretes a number of important hormones for the reproduction. In the anterior hypophysis, gonadotropic hormones are secreted,

such as LH (luteinizing hormone) and FSH (follicle-stimulating hormone). The hypothalamus produces the GnRH (gonadotropin-releasing hormone), which promotes the liberation of the LH and FSH. These hormones are important for the growth of follicles after menstruation and also for ovulation. After the occurrence of ovulation, the LH also induces the ruptured follicle to form the endocrine corpus luteum. The granulosa cells of the ruptured follicular wall begin to proliferate and give rise to the cells of the corpus luteum. With this viewpoint, two basic mechanisms can be considered for the performance of the substances in these areas (Farnsworth *et al.*, 1975):

- Interference of a normal hormonal function of the hypothalamus and pituitary by steroids, non-steroids with anti-gonadotropic activity, and by steroid antagonists
- Interference of the neural impulse for the hypothalamus

Several plant extracts are used by folk medicine and they may act on the hypothalamus, such as *Juniperus communis* and *Physalis alkekengi* fruit extracts (Table I). These extracts were respectively administered by oral and intraperitoneal routes of administration on rats. Both presented an anti-fertility effect, and the authors verified that these plants interfered with the hypothalamus, suggesting a possible action mechanism (Prakash *et al.*, 1994; Vessal *et al.*, 1991).

Ovary

The chemical substances may exert their anti-fertility effects at ovarian level by the inhibition of the ovulation and the synthesis of steroids. The corpus luteum secretes large quantities of estrogen and progesterone, while the inhibin hormone presents a negative feedback for the liberation of LH and FSH. The performance of the substance in the corpus luteum can interfere with the synthesis of steroids. Some substances also can act impeding the ovulation, for example, the prostaglandin. These substances reach the corpus luteum and decrease the ovarian secretion of progesterone.

Rivea hypocrateriformis is an example of plant that reaches the ovarian structure. The ethanol extract of the aerial parts of this plant when tested in female albino rats caused anti-fertility activity due to the anti-progestational effect, which might act as inhibitor either in the biosynthesis of progesterone or in the receptor binding (Shivalingappa *et al.*, 2001).

There is folk information regarding women seated briefly above a bath of the plant *Inula viscosa* three days after copulation, or had administered ground leaves through the anus for abortifacient purpose. However, no experimental studies have been found supporting the reputed pregnancy terminating action of *I. viscosa*. An

experimental study showed that an aqueous extract of leaf of this plant caused a significant reduction in the number of corpus luteum and of progesterone blood levels (Dafni *et al.*, 1984; Al-Dissi *et al.*, 2001).

Choudhur *et al.* (1991) administered an ethanolic extract of *Piper betle* (1g/kg) in rats and observed a decrease in the activity of the responsible enzyme for the synthesis of steroid hormones. Besides that, this plant diminishes the number of corpus luteum. The authors concluded that these explanations might probably justify the folkloric use of *Piper betle* to cause abortion.

Oviduct

A normal embryonic implantation in the uterus depends on the exact time of embryonic arrival on the uterus. However, if there are complications in the ovum transportation in the oviduct, there will be some miscues during the implantation. The substances that have the ability of altering the motility of the oviduct, may be able to inhibit the fertility and the embryonic implantation, as verified by Singh *et al.* (1993) (Table I), when administered the ethanol extract of *Ixora finlayconiana* (1g/kg) in rats in the first day of pregnancy.

Boling and Blandau (1971) demonstrated that smooth musculature of the reproductive tract exhibits maximum contractility under estrogenic influence, and it has been related that several plants possess estrogenic activity.

Estrogen and progesterone can also alter fertility. The estrogen increases the synchronized beating of the cilia on the oviduct wall, carrying the ovum on the direction of the uterus, and it also relaxes the isthmus for the passage of the ovum. Therefore, an altered dose of these hormones can increase or decrease the exact arrival time of the zygote in the uterus. The isthmus of rabbits, rats and humans possess a rich sympathetic innervation, maintaining the sphincter tonus of the isthmus, promoting the ovum retention. So, the substances that affect the SNA sympathetic can interfere with fertility (Farnsworth *et al.*, 1975).

Lemonica *et al.* (1996) verified that *Rosmarinus officinalis* aqueous extract (Table I) interfered with the oviduct movements and consequently with ovum transport, or with the uterine condition related to ovum implantation. Damasceno and Lemonica (1999) showed that the rats treated with 260 mg/kg of *R. officinalis* aqueous extract presented embryotoxic effect and 1040 mg/kg promoted a longer embryo retention in the oviduct. Similarly, Almeida and Lemonica (2000) showed that leaf extract of *Coleus barbatus* (boldo) caused an anti-implantation effect, as shown in Table I.

Table 1 – Antifertility plants evaluated in experimental animals

Plant Name	Popular Name	Part	Type of Extract	Dose	Route of Administration	Species	Structure	Reference
<i>Abrus precatorius</i>	Jequiriti	Seeds	PE	150 mg/kg	-	Rats/Mice	O	Zia-Ul-Haque et al. (1993)
<i>Acacia catechu</i>	Catechu	Fruit	PE	100-500 mg/kg	oral	Rats	-	Garg & Garg (1970)
<i>Acalypha indica</i>	Erva daninha	Whole plant	PE and ET	300-600 mg/kg	oral	Rats	U	Hiremath et al. (1999)
<i>Adhatoda vasica</i>	-	Leaf	vasicine	5 mg/kg	ip	hamster	U	Claesson et al. (2000)
<i>Ailanthus excelsa</i>	Árvore celeste	Leaf and Stem bark	ET	250 mg/kg	oral	Rats	-	Dhanasekaran et al. (1993)
<i>Ambrosia artemisiifolia</i>	Ambrosia americana	Plant	W	-	-	Rat	T	Mats et al. (1987)
<i>Anona squamosa</i>	Pinha	Seed	W	100 mg/kg	oral	Rat	-	Mishra et al. (1979)
<i>Aristolochia indica</i>	Papo de Peru	Roots	ET	50 mg/kg	oral	Mouse	-	Pakrashi & Pakrashi (1979)
<i>Artemisia absinthum</i>	Losna	Leaves	ET	200 mg/kg	oral	Rats	-	Rao et al. (1988)
<i>Atejea glazioviana</i>	Timbo de palmeira	Leaf	W	100 mg/kg	i.p.	Rats	-	Marona et al. (1992)
<i>Azadirachta indica</i>	Cinamomo ou Nimbo	Seeds	HE	100% fraction (NS101/H)	oral	Rats	-	Mukherjee & Talwar (1999)
<i>Cannabis sativa</i>	Maconha	Leaves	W	125-200-400-800 mg/kg	oral	Rats	-	Sethi et al. (1991)
<i>Carica papaya</i>	Mamoeiro	Fruits	PE	500 mg/kg	oral	Rats	-	Garg (1974)
<i>Cassia fistula</i>	Cannafistula verdadeira	Seeds	W	500 mg/kg	oral	Rats	U	Yadav and Jain (1999)
<i>Cinnamomum zeylanicum</i>	Canela	Leaf	W and CH	70 mg/kg	oral	Rats	-	Lemonica & Macedo (1994)
<i>Citrusulocyclynthus</i>	Coloquintida verdadeira	Leaf	ET and BZ	-	-	Rats	-	Prakash et al. (1985)
<i>Citrus hystrix</i>	Limeira da Pérsia	Fruit peel	ET and CH	100 mg for 5g/kg	oral	Rats	U	Piyachaturawat et al. (1985)
<i>Coleus barbatus</i>	Boldo	Leaf	ETW	880 mg/kg	oral	Rats	O or T	Almeida and Lemonica (2000)
<i>Coriandrum sativum</i>	Coentro	Seeds	W	250-500 mg/kg	oral	Rats	O	Al-Said et al. (1987)
<i>Croton cajucara</i>	Cajucára	Bark	l-dehydrocrotinin	25-50 mg/kg	oral	Rats	U	Luna Costa et al. (1999)
<i>Cuminum cyminum</i>	Cominho	Seeds	W	250 and 500 mg/kg	oral	Rats	O	Al-Kamis et al. (1988)
<i>Daucus carota</i>	Cenoura	Seeds	ET	50 to 250 mg/kg	oral	Rats	U	Bhatnagar et al. (1995)
<i>Dimorphandra mollis</i>	Barbatimão	Pods	ETW	2 g/kg of dried plant	oral	Rats	-	Langeloh et al. (1991)
<i>Gossypium herbaceum</i>	Algodão	Seeds	W	200 mg/kg	oral	Rats	-	Nath et al. (1997)
<i>Hibiscus rosa sinensis</i>	Mimo-de-vênus	Flowers	BZ	1 mg/kg	oral	Mouse	O	Pakrashi et al. (1986)
<i>Himanthanthus succuba</i>	Sucuuba	Stem bark	W	40 mg/day	oral	Rats	-	Guerra & Peters et al. (1991)
<i>Inula viscosa</i>	-	Leaf	W	1.86 mg/kg	oral	Rats	O	Al-Disse et al. (2001)
<i>Ipomoea fistulosa</i>	Algodão bravo	Aerial parts	ET	100 mg/kg	oral	Rats	-	Mishra et al. (1979)
<i>Ixora finlaysoniana</i>	Ixora branca	Aerial parts	ET	250-500-1000 mg/kg	oral	Rats	O or T	Singh et al. (1993)
<i>Jatropha curcas</i>	Pinhão-de-purga	Fruit	Different extracts	Different doses	oral	Rats	-	Mishra et al. (1995)
<i>Juniperus communis</i>	Zimbro	Needles	-	4.5-5.5 kg/d	oral	Cattle	U or T	Gardner et al. (1998)
<i>Kigelia pinnata</i>	Madeira Idolo	Fruit	B	100- 400 mg/kg	oral	Rats	H or O	Prakash et al. (1994)
		Plant	ET	-	-	Rats	-	Prakash et al. (1985)

<i>Mentha arvensis</i>	Hortelã	Seeds	W	175 mg/kg	oral	Rats	O	Sethi et al. (1989)
<i>Murraya paniculata</i>	Jasmim Laranja	Roots	ET	100 mg/kg	oral	Rats	O	Choudhuri et al. (1990)
<i>Nelumbo nucifera</i>	Lotus do Egito	Seeds	PE	3 mg/kg	i.p.	Mice	O	Mazumber et al. (1992)
<i>Nigella sativa</i>	Nigela	Seeds	HE	2 g/kg	oral	Rats	U	Keshri et al. (1995)
<i>Ocimum sanctum</i>	Mangericão	Leaves	PE, BZ, E, AC	1 mg/kg	oral	Rats	-	Batta et al. (1971)
<i>Paeonia officinalis</i>	Erva de Santa Rosa	Leaves	W	175 mg/kg	oral	Rats	-	Sethi et al. (1989)
<i>Philanthus amarus</i>	Quebra-pedra	Whole plant	ET	100 mg/kg	oral	Mice	O	Rao and Alice (2001)
<i>Physalis alkekengi</i>	Camapu	Fruits	W	1ml/day	i.p.	Rats	H or U	Vessal et al. (1991)
<i>Piper betle</i>	Merita	Leaves	ET	1 g/kg	oral	Rats	O	Choudhuri et al. (1990)
<i>Plisum sativum</i>	Ervilha	Seeds	m-xylohydroquinilone	20-30% of diet	oral	Rat	-	Sanyal (1956)
<i>Rinicus comunis</i>	Mamão	Seeds	ME	600 -1.2 mg/kg	subcutaneous	Rats	-	Okwasaba et al. (1991)
<i>Rivea hipocrateriformis</i>	-	Aerial parts	ET	200-400 mg/kg	oral	Rats	O	Shivalingappa et al. (2001)
<i>Rosmarinus officinalis</i>	Alecrim	Aerial parts	W	130mg/kg	oral	Rats	O or T	Lemonica et al. (1996)
<i>Ruta graveolens</i>	Arruda	Leaves	ET	125 mg/kg	oral	Rats	T	Rao et al. (1988)
<i>Schubertia multiflora</i>	Angélica de Rama	Roots	ET	80 mg/kg	oral	Rats	-	Rao et al. (1988)
<i>Sida carpinifolia</i>	Vassourinha	Whole plant	ME	20 mg/rat	oral	Rats	U	Khoikute & Munshi (1978)
<i>Sida linifolia</i>	Guaxuma	Leaves	ET	25 mg/kg	oral	Rats	-	Nwobodo et al. (1996)
<i>Sida veronicaefolia</i>	Guanchumba	Aerial parts	ET	different doses	different routes	Rats	U	Lutterodt (1988)
<i>Spondias mombin</i>	Cajazeira	Leaves	W	750-1500mg/kg	i.p.	Mice	-	Offiah & Anyanwu (1989)
<i>Stevia rebaudiana</i>	Caá-ehé/ Stévia	Weeds	W	5ml/kg	oral	Rats	-	Planas & Kuc (1968)

Types of extract: W=aqueous; PE=petroleum ether; ET= ethanol; E= ether; CH= chloroform; BZ= benzene; B= butanolic; ME= methanolic; AC= acetone; HE= hexane; ETW= ethanol-water.
Structures: H=hypothalamus; O=ovary; T= oviduct; U= uterus.

Uterus

In the uterus, the estrogen will have the function of altering the endometrium, bringing on a proliferation of the stroma and a great development of glands. The progesterone stimulates the endometrial layer to thicken further and to form glandular structures and increased vasculature, that are necessary for the nutrition of the zygote, which is in division. It also diminishes the uterine contractions, helping to impede the excretion of the ovum implanted. Therefore, the substances that act altering the concentration of estrogen and progesterone may have an anti-implantation or abortifacient effect, likewise the substances that stimulate the uterine contraction (Guyton and Hall, 1997).

Hiremath *et al.* (1999) investigated the petroleum ether and ethanol extracts of the *Acalypha indica* (weed) in female rats and found to be an effective agent to cause significant anti-implantation activity and suggested an estrogenic effect of this plant. This effect was observed in morphological studies of the uterus morphometry. This paper appears contradictory because an early embryo needs an edematous uterine wall, vascularized, to support the growth of the embryo implanted, which is realized by a high estrogenic level.

The Table I shows some plants that act in the uterus such as *Citrus hystrix*. According to Piyachaturawat *et al.* (1985) the rats treated with alcohol and chloroform extracts of the *Citrus hystrix* presented the blastocysts excreted due to an increase of uterine contractions, and this fact might to justify the use of this plant for the Brazilian women as an abortifacient.

It is a common misconception that "all that is natural is good", and a number of highly toxic compounds have been isolated from plants. The lack of information about other toxic effects of many plants used as abortifacient justify the investigation about their wide use. Before these medicinal plants may be used in humans, further scientific research is required. Toxicological and clinical studies, that support the use of these plants, confirm that anti-fertility activity study should be made. On the other hand, we would like to suggest further chemical-pharmacological studies using plants that would lead us to identification of the responsible substance(s) for the anti-fertility effect, and the mechanism by which the plant extract influences in the reproduction.

CONCLUSION

From the data presented in Table I, it can be seen that a number of plants are known to have a folkloric reputation for use as abortifacient or contraceptive during the pregnancy. But the plant extracts frequently have not had their effects

confirmed in laboratory animals. This fact might be related to differences of sensibility in, and between, species, the treatment periods which the women and the experimental animals are undergoing, the dose employed and the preparation of the plant extract used. Furthermore, the species of plants used can contain different isolated active compounds. Presumably, these active principles might produce anti-fertility effect or exhibit no action on the reproductive functions.

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