

Antifertility effects of herbs: Need for responsible reporting

Amit Agarwal, Joshua J. Allan

R & D Centre, Natural Remedies, Bangalore, India

ABSTRACT

Evaluation of herbs for antifertility effects has been in progress worldwide for several decades to identify effective and safe substances for control of population explosion. In spite of availability of internationally accepted guidelines for the assessment of reproductive toxicity/antifertility potential of test substances, many published articles, on critical review, seem to lack reproducibility and are thus likely to mislead both the scientific community and the general public. This paper, while emphasizing the importance of generating authentic toxicity/safety information on acclaimed medicinal herbs, spells out existing pitfalls in such studies, and explores some control measures worth considering in times to come.

Key words: Antifertility, toxicity, herbal toxicity

INTRODUCTION

Medicinal plants in India have been screened for contraceptive potential and anti-fertility effects, since the country has always been concerned about population explosion. The probable male/female antifertility effects arising from short or long term exposure of certain common and valuable Indian medicinal plants are published in scientific literature; but unfortunately, the outcomes of research investigations are more often complicated by scientists' compulsions to report positive results.

As Rob Verpoorte (Editor-in-Chief, *Journal of Ethnopharmacology*) emphasizes, "We must be objective in reporting our results, if one measures an activity in the mM range for a pure compound or mg/ml range for an extract, that is a finding, a number, but it does not mean that we can say that a compound or extract is active, or has an activity. That can only be discussed by comparing the results with proper controls and also taking into account the assays used."^[1] A cursory look at the published reproductive toxicity studies on a few medicinal herbs not only draws attention to the contradictory findings by

various investigators, but also the startling differences in terms of test substances used, their standardization, and adopted test methodologies etc.^[2-7]

Detailed description of herbal extract/formulation in scientific papers now seems to be essential, and no longer "add-on information," since peer-reviewed journals of international repute consider them mandatory requirements. The journal *Phytomedicine* (*International Journal of Phytotherapy and Phytopharmacology*), in its "instructions to authors," explains that "the extract being reported with pharmacological activity must have some type of standardization. The standardization can be carried out by means of a High Performance Liquid Chromatography (HPLC) fingerprint or quantitative assessment of known bioactive compounds. A qualitative HPLC-fingerprint analysis for extracts whose bioactive constituents are unknown may be used". Without standardization of an extract, the journal further states that results cannot be accepted for publication.^[8] *Planta Medica*, another leading journal in the field of medicinal plants, considers papers for publication only if preparation of the extracts is clearly described and supported with adequate analytical studies.^[9] Researchers should ensure that herbal extracts and formulations are prepared properly and well standardized for contents of pesticides, heavy metals, mycotoxin, solvent, and microbial residues, since these may create doubts as to whether adverse reproductive effects are induced by herbal constituents or by contaminants. Significantly, a good number of published articles that have "declared" certain herbs to be antifertility agents sorely lack this vital information. Such seemingly well-intended research papers have done more harm than good to ethnopharmacology and traditional medicine.

Address for correspondence:

Dr. Amit Agarwal,
Natural Remedies, Plot No. 5B, Veerasandra Industrial Area,
19th K. M. Stone, Hosur Road, Bangalore - 560 100,
Karnataka, India.

E-mail: amit@naturalremedy.com

Received: 25-Nov-2009

Revised: 09-Mar-2010

Accepted: 20-Mar-2010

DOI: 10.4103/0975-9476.65092

Fransworth and Waller (1982) reviewed the status of a number of plant products reported to inhibit sperm and observed contradictions that existed between findings of different researchers, “*in-vitro*” vs. “*in-vivo*” data, and also between scientific studies and traditional knowledge. They also summarized insufficient numbers of vehicle controls, poor experimental design, difficulties encountered in dissolving crude herbal extracts, different routes of administration, and variations in reproductive function among different experimental animals, as important aspects complicating the accurate assessment of effects of herbs on male fertility.^[7] Since several reproductive toxicity studies of the recent past were conducted according to a custom-made approach, and many times not in conformity with internationally accepted guidelines for reproductive/fertility studies, the aforementioned factors could potentially have influenced study outcomes either way.

In addition, such misleading information often attracts the attention of regulators since, in the regulatory framework, toxicity evaluation can have direct impact on restriction or removal of the herbal ingredients. Alternatively, they may lead to demands for additional safety data. Due to the lack of adequate toxicity data or existence of contrary reports on the substance under consideration, international regulatory agencies generally adopt a cautious approach, until enough scientific information is generated which can mitigate the uncertainty associated with the safety of consumption of such herbal preparations.^[10]

In Australia, the Complementary Medicine Evaluation Committee (CMEC) of Therapeutic Goods Administration (TGA), once objected to registration of Triphala, a polyherbal Ayurvedic formulation, based on a study which reported male reproductive toxicity on oral use of *Terminalia bellirica* extract (one of the three ingredients of the traditional formulation).^[11] Although the findings of the study were “successful demonstration” of contraceptive efficacy, the practical outcome turned out to be quite contrary. Consistent efforts towards generation of scientific data in subsequent years finally saw the TGA permitting inclusion of *T. bellirica* in the Australian Register of Therapeutic Goods (ARTG), thereby enabling export of such Ayurvedic products to Australia.

Another classical example is Brahmi (*Bacopa monnieri*), a popular herb with a cognition enhancing effect. Evaluation of antifertility potential of an aqueous extract of Brahmi in male mouse revealed *reversible* male infertility; but, as stated elsewhere, the phytochemical and analytical specifications were not mentioned. Also, the study observed that the percentage of affected seminiferous tubules in the testis was 96.27% after 28 days of Brahmi treatment vs. 54.13% after 56 days of treatment and this observation, as a result, leads to contention.^[12]

Effects of *Ocimum sanctum* on reproductive systems of laboratory animals have attracted scientists globally, and extensive toxicological studies have been carried out, particularly on rats of both sexes. The early abortifacient effect of *O. sanctum* supplementation recorded by researchers during 1950s was later shown to be non-reproducible.^[13] As discussed earlier, some studies on *O. sanctum* or isolated compounds of *O. sanctum* were conducted using test material not properly standardized for purity, adopted the route of administration that is not commonly intended for the test material, or lack the rationale for appropriateness of the doses and duration of treatment used.^[14-17] From established guidelines for reproductive toxicity studies, it can be observed that confirmation of the toxic potential of a test substance on fertility requires treatment of sufficient duration, a fact that seems to be “conveniently forgotten” by some investigators. Also, adverse effects in terms of transient, reversible or irreversible nature, need to be given due consideration before declaring unsafe herbs, which are otherwise relatively safe.

The observations on published literature on *Andrographis paniculata* may provide noteworthy insights in this regard. Even though *A. paniculata* is used in many hepatoprotective formulations in India, global acceptance warranted published scientific evidence in reputed journals. For quite some time, preclinical studies on *A. paniculata* have reported probable male and female antifertility effects following oral administration. However, previous investigations of rats/mice were based on oral administration of crude leaf powder of *A. paniculata* for 60 days. The phytochemical and analytical specifications of the test materials were found to be lacking in most of the published articles. Furthermore, the data on critical endpoints like sperm concentration, sperm motility, and testosterone levels were not available for possible comparison with such similar works.^[2] Burgos *et al.* (1998), with the aid of electron microscopic observations, disproved the earlier, conventional microscopic findings of disruption of testicular histology by treating male rats with *A. paniculata* extract (containing 6.1% andrographolide) up to 1000 mg/kg for 60 days,^[3] while a phase I clinical study by Mkrtychyan *et al.* (2005) found the semen quality of healthy male subjects remained unaffected upon treatment with three times the therapeutic dose level of *A. paniculata* fixed combination (180 mg of andrographolide daily for 10 days) and validated the safety of the herb.^[4] In another study, female mice were administered with feed mixed-sundried powder of *A. paniculata* and the dose employed was 2 g/kg per day for 6 weeks^[6] – a dose level that OECD recommends for testing of substances in acute oral toxicity studies!^[18] Similar observations indicated that several authors of reproductive toxicity studies often do not correlate doses that can produce reproductive toxicity from dose levels normally administered in Ayurveda,

Siddha and Unani (ASU) medicine. The famous dictum of Paracelsus (1493–1541) that “the dose makes the poison” should always be remembered before declaring any substance as unsafe.

Considering the importance of *A. paniculata* as a precious herbal remedy, Allan *et al.* (2009) reported in *International Journal of Toxicology* the findings of a study conducted taking into consideration internationally accepted guidelines. The authors reported that male rats orally administered with an extract of *A. paniculata* ($\geq 10\%$ andrographolide) up to the dose level of 1000 mg/kg daily for 86 days did not show any adverse effects in sperm parameters such as sperm concentration and sperm motility. The serum testosterone levels of treated rats were comparable to that of control rats and there were no gross and histopathological changes in testes and epididymides. The male rats, after 65 days of treatment with *A. paniculata* extract, were mated with females and produced healthy offspring.^[5] It appears that similar corrective studies are essential for other important medicinal plants as well.

In summary, publishing dubious antifertility effects of beneficial herbs not only leads to huge economic impact on industry for disproving the same, but also adversely affects traditional medicine’s credibility. If so many plants were found to have antifertility effects, then where are the drugs made from them? Dose–response relationship is indeed crucial; however, convincing regulatory authorities after someone publishes conflicting reports, may be a phenomenal task. Hence, sufficient efforts should be directed to draw attention to this perplexing problem. Steps should be taken to prevent its recurrence. Adequate awareness has to be created among researchers toward developing the concept, designing, executing, interpreting, and reporting the findings of reproductive/antifertility studies in accordance with internationally accepted guidelines. This critical issue needs attention of all the funding agencies supporting research on natural products with an ethnomedical basis. Overall there is a need to promote genuine, reproducible findings based on sound scientific principles, and, at the same time, discourage publication of outcomes of studies falling short of basic and reliable research requirements. In addition to researchers and funding agencies, this point needs attention from custodians of published scientific research viz. editors, reviewers, and editorial board members of scientific journals. If such precautions are exercised at the level of researchers, funding agencies, and the publishing community, we shall together ensure that research declaring herbs to be “safe” or “toxic” is responsible and reliable.

REFERENCES

1. Verpoorte R. Newsletter 7. J Ethnopharmacol. Available from: http://www.elsevier.com/framework_products/promis_misc/jepreviewers0809.pdf [Last cited on 2009]
2. Akbarsha MA, Manivannan B, Hamid KS, Vijayan B. Antifertility effect of *Andrographis paniculata* (Nees) in male albino rat. Indian J Exp Biol 1990;28:421-6.
3. Burgos RA, Caballero EE, Sanchez NS, Schroeder RA, Wikman GK, Hancke JL. Testicular toxicity assessment of *Andrographis paniculata* dried extract in rats. J Ethnopharmacol 1997;58:219-24.
4. Mkrtchyan A, Panosyan V, Panossian A, Wikman G, Wagner H. A phase I clinical study of *Andrographis paniculata* fixed combination Kan Jang™ versus ginseng and valerian on the semen quality of healthy male subjects. Phytomedicine 2005;12:403-9.
5. Allan JJ, Pore MP, Deepak M, Murali B, Mayachari AS, Agarwal A. Reproductive and fertility effects of an extract of *Andrographis paniculata* in male Wistar rats. Int J Toxicol 2009;28:308-17.
6. Zoha MS, Hussain AH, Choudhury SA. Antifertility effect of *Andrographis paniculata* in mice. Bangladesh Med Res Council Bull 1989;15:34-7.
7. Fransworth NR, Waller DP. Current status of plant products reported to inhibit sperm. Res Front Fertil Regul 1982;2:1-16.
8. Phytomedicine (International Journal of Phytotherapy and Phytopharmacology). Elsevier. Available from: http://www.elsevier.com/wps/find/journaldescription.cws_home/701794/authorinstructions [Last 2009 Feb 18].
9. Planta Medica (Journal of Medicinal Plant and Natural Product Research). Official organ of the Society for Medicinal Plant and Natural Product Research. Thieme Journals. Available from: http://www.thieme.de/fz/show_pdf.html?fz/plantamedica/Planta_Medica_Guidelines.pdf [Last 2009 Feb 18].
10. Jordan SA, Cunningham DG, Marles RJ. Assessment of herbal medicinal products: Challenges, and opportunities to increase the knowledge base for safety assessment. Toxicol Appl Pharmacol 2010;243:198–216.
11. Rao MV. Effects of alcoholic extract of *Terminalia bellirica* fruit extract on male reproductive functions. Arch Biol (Bruxelles) 1989;100:37-46.
12. Singh A, Singh SK. Evaluation of antifertility potential of Brahmi in male mouse. Contraception 2009;79:71-9.
13. Ahmed M, Khan MY, Khan AA. Effects of *Ocimum sanctum* (Tulsi) on the reproductive system: An updated review. Biomed Res 2002;13:63-7.
14. Vohora SB, Garg SK, Chaudhury RR. Antifertility screening of plants. 3. Effect of six indigenous plants on early pregnancy in albino rats. Indian J Med Res 1969;57:893-9.
15. Kasinathan S, Ramakrishnan S, Basu SL. Antifertility effect of *Ocimum sanctum* L. Indian J Exp Biol 1972;10:23-5.
16. Akbarsha MA, Palanisamy M, Murugaian P, Lakshmi Latha PN. Ursolic acid generates symplasts in rat spermatogenic clones. Phytother Res 1998;12:32-6.
17. Kantikant NM, Gogate MG. Effect of short term administration of Tulsi (*Ocimum sanctum* Linn.) on reproductive behaviour of adult male rats. Indian J Physiol Pharmacol 1992;36:109-11.
18. Organisation for Economic Co-operation and Development (OECD). OECD guideline for testing of chemicals: Guideline 420, Acute Oral Toxicity - Fixed Dose Procedure, OECD, Paris, France, 2001.

Source of Support: Nil, Conflict of Interest: None declared.