



Review Article

Safety Uses of Phytomedicines in Pregnancy and Pediatrics: An Overview***Sachan Anupam K, Pujari Neelkanth M****Dayanand Dinanath College, Institute of Pharmacy, Kanpur-209214, INDIA**

Received: 23 Jan 2015

Revised: 19 Feb2015

Accepted: 24 Feb 2015

ABSTRACT: During the last decade, there has been a dramatic rise in the availability and use of medicinal herbal preparations. Medical journals are now publishing case reports of adverse reactions to herbal therapy. With increasing use, and more importantly, increasing awareness of potential hazardous effects, these reports are liable to increase in frequency. It has been found that herbs and drugs can interact in the same way as drug/drug interactions occur. All medicinal agents have potentially unexpected effects including toxicity and interactions and herbs are no different. Drug-herb interactions are based on the same pharmacokinetic and pharmacodynamic principles as drug-drug interactions. The data existing for most plants to guarantee their quality, efficacy and safety is insufficient. The concept that herbal drugs are safe and free from side effects is not always true. Harmonization and improvement in the process of regulation is needed for safety aspects related to phytomedicines. During pregnancy it can be dangerous to consume some herbs and herbal remedies. Some herbs contain steroids that can affect the baby's development during pregnancy and/or nursing. Many women turn to herbal remedies during pregnancy for nausea and uterine tonics. Infants and children may be even more susceptible to some of the adverse effects and toxicity of these products because of differences in physiology, immature metabolic enzyme systems, and dose per body weight. Although information promoting the use of herbal medicine is widespread, true evidence-based information about the efficacy and safety of herbal medications is limited.

Keywords: Herbs, Interactions, Safety, Pregnancy, Children

INTRODUCTION:

According to the World Health Organization [WHO;2001], phytomedicine is defined as herbal preparations produced by subjecting plant materials to extraction, fractionation, purification,

concentration or other physical or biological processes. These preparations may be produced for immediate consumption or as the basis for other herbal products. Such plant products may contain recipient or inert ingredients, in addition to the active ingredients. Data from the World Health Organization (WHO) shows that more than a half of the world population makes use of some type of medicinal herb searching for relief for painful or

Address for Correspondance:

Anupam Kr Sachan
Dayanand Dinanath College, Institute of Pharmacy,
NH#86, Hamirpur Road, Ramaipur,
Kanpur-209214, INDIA
Contact: +91-9936273358
E-mail: anupamkrsachan@gmail.com

unpleasant symptoms. From that total at least 30% are provided by medical prescription.[WHO;2009]

Many of the pharmaceuticals currently available to physicians have a long history of use as herbal remedies, including opium, aspirin, digitalis, and quinine. The World Health Organization (WHO) estimates that 80 percent of the world's population presently uses herbal medicine for some aspect of primary health care. Herbal medicine is a major component in all traditional medicine systems, and a common element in Ayurvedic, homeopathic, naturopathic, traditional Chinese medicine, and Native American medicine. The World Health Organization (WHO) has listed 21,000 plants, which are used for medicinal purposes around the world. Among these 2500 species are in India, out of which 150 species are used commercially on a fairly large scale. India is the largest producer of medicinal herbs and is called as botanical garden of the world.[Seth;2004]

In India the herbal remedy is so popular that the government of India has created a separate department AYUSH under the Ministry of Health & Family Welfare. The National Medicinal Plants Board was also established in 2000 by the Indian government in order to deal with the herbal medical system.[Kala;2007] The use of herbs to treat disease is almost universal among non-industrialized societies.

For years, public interest has increased for natural therapies (mainly phytomedicine) all over the world.[Blumenthal;1999] There are several factors that lead to the preference and growth of phytotherapeutic market worldwide and they include

preference of consumers for natural therapies, belief that phytomedicine is devoid of side effect since millions of people all over the world have been using phytomedicine for thousands of years, also that phytomedicine is used for the treatment of certain diseases where conventional medicine fails and high cost of synthetic drugs.[Okigbo;2006]

A number of herbs are thought to be likely to cause adverse effects. Furthermore, "adulteration, inappropriate formulation, or lack of understanding of plant and drug interactions have led to adverse reactions that are sometimes life threatening or lethal.[Elvin-Lewis;2001]" Proper double-blind clinical trials are needed to determine the safety and efficacy of each plant before they can be recommended for medical use.[Vickers;2007] Although many consumers believe that herbal medicines are safe because they are "natural", herbal medicines and synthetic drugs may interact, causing toxicity to the patient. Herbal remedies can also be dangerously contaminated, and herbal medicines without established efficacy, may unknowingly be used to replace medicines that do have corroborated efficacy.[Ernst;2007]

However, herbal supplements haven't been subjected to the same scientific scrutiny and aren't as strictly regulated as medications. For example, although makers of herbal supplements must follow good manufacturing practices — to ensure that supplements are processed consistently and meet quality standards — they don't have to get approval from the Food and Drug Administration (FDA) before putting their products on the market.

Yet all herbs including herbal supplement products labeled as "natural" can have drug-like effects. Anything strong enough to produce a positive effect, such as lowered cholesterol or improved mood, is also strong enough to carry risk. [Mayo;2014]

Unlike conventional drugs, herbal products are not regulated for purity and potency. [Indiahomeclub;2008] Thus, some of the adverse effects and drug interactions reported for herbal products could be caused by impurities (e.g., allergens, pollen and spores) or batch-to-batch variability. In addition, the potency of an herbal product may increase the possibility of adverse effects.

Herbal medicinal products in some cases compromise the efficacy of conventional medicine, for example through herb-herb interactions, herb-drug interactions or herb-food interactions. [Ernst;2000] Similarly like drugs do, the interactions may increase or decrease the effectiveness and/or the side effects of the drugs. It may also result in new side effect, i.e. a side effect that is not seen with any one drug/herb alone. A common misconception about herbalism and the use of "natural" products in general, is that "natural" equals safe. Herbs can also have undesirable side-effects just as pharmaceutical product can.

The past decade has also witnessed intense interest in "nutraceuticals" (or "functional foods") in which phytochemical constituents can have long-term health promoting or medicinal qualities. Although the distinction between medicinal plants and nutraceuticals can sometimes be vague, a primary characteristic of the latter is that nutraceuticals have

a nutritional role in the diet and the benefits to health may arise from long-term use as foods (i.e. chemoprevention). [Korver;1998] In contrast, many medicinal plants exert specific medicinal actions without serving a nutritional role in the human diet and may be used in response to specific health problems over short- or long-term intervals. [Donald;2000]

Some herbal remedies have the potential to cause adverse drug interactions when used in combination with various prescription and over-the-counter pharmaceuticals. Dangerously low blood pressure may result from the combination of an herbal remedy that lowers blood pressure together with prescription medicine that has the same effect. In particular, many herbs should be avoided during pregnancy. [gaiagarden;2008] The reported prevalence of herbal use is higher among women than among men.

Although not frequent, adverse reactions have been reported for herbs in widespread use. [Pinn;2001] On occasion serious untoward outcomes have been linked to herb consumption. A case of major potassium depletion has been attributed to chronic licorice ingestion [Lin;2003] and consequently professional herbalists avoid the use of licorice where they recognize that this may be a risk. Black Cohosh has been implicated in a case of liver failure. [Lynch;2006] Few studies are available on the safety of herbs for pregnant women, [Born;2005][gaiagarden;2008] and one study found that use of complementary and alternative medicines are associated with a 30% lower ongoing pregnancy

and live birth rate during fertility treatment.[Boivin;2009]

Herbal Products in Pregnancy

A number of herbs could cause adverse effects due to adulteration, inappropriate formulations, plant and drug interactions, effects that are sometimes life threatening or lethal. Patients who are likely to be at risk from adverse effects of herbal medicines include those who are already prone to difficulties from orthodox medications including the fetus, infants, pregnant and lactating women. [Conover;2003] While pregnant women and their health care providers are increasingly aware that they should avoid unnecessary exposures during pregnancy, a paradoxical increase in the quantity of self administered herbal and over the counter(OTC) medication have been reported. Majority of the traditional herbal medicines used are provided by practitioners who live within the communities, have been trusted over time and are often willing to assist the patients with their knowledge and skills, sometimes at minimal costs to the patients. Most of these herbal medicines are procured in their crude forms although some pharmaceutical prepackaged forms also exist and are available over the counter. Herbal use among pregnant women raises particular concerns of safety. These safety concerns have been attributed to the herbal ingredients itself [Dietary Supplement;2008], interactions between a herbal product and other pharmaceuticals (example, ginseng and insulin)[Dugoua;2006] and contamination of products by unlabeled toxins (example, lead and mercury).[Ko;1998]

In spite of these known concerns, many patients do not disclose use of herbal medicines to their health care providers [Broussard;2010], although some herbal use by pregnant women have been reported to have been recommended by health care providers, natural or alternative health care providers, pharmacists, friends or family and even in response to information from media sources.[Tamuno;2010]

In addition to these concerns, poor regulatory framework for importation, manufacturing and distribution of herbal medicines in Africa keeps herbal medicine poorly researched where even the registered products do not adhere to GMP principles of safety and efficacy as is required for conventional medicines.[Tsui;2001]

Safety Issues after maternal herbal consumption during pregnancy and/or lactation

Pregnancy is a time of rapid physical and emotional changes in the body. Herbs can be very useful in toning and nourishing the system to help allay potential problems and remedy discomforts that pregnant women may experience. Attention to nutrition can go a long way in preventing possible complications. Mood swings and morning sickness, which are quite common, are connected to low blood sugar. A lack of Calcium can result in hypertension, backaches and severe labor pains. Malnutrition during pregnancy can cause constipation, hemorrhoids, anemia, and even pre-eclampsia. It's absolutely vital to get enough vitamins, minerals and protein during pregnancy.[Marcus;2005]

Medicinal Plants (herbs) in their original form contain a host of natural ingredients—alkaloids,

bioflavonoids, glycosides, minerals, vitamins, volatile oils, and other natural substances that not only support an herb's healing benefits but also safeguard against potential toxicity. Natural herbs can be very beneficial during pregnancy. It is important however you realize that just because something is natural doesn't necessarily mean it is safe. There are some herbs that are harmful to pregnant mothers and their babies. Herbal remedies are considered natural alternatives to certain drugs, but they can also be dangerous when taken during pregnancy. While a cup of chamomile tea is perfectly safe for a mum-to-be, many herbs contain chemicals that can cross the placenta to your baby, and some can cause premature contractions.

Although herbs are not necessarily needed by all women during pregnancy, certain herbs are recommended by experienced herbalists and have been used safely by women for centuries. It is important to consult with doctor or healthcare provider or qualified herbalist prior to using any herbs in pregnancy or while breastfeeding. Some herbs are safe to use during pregnancy but not all are. That is why it is important to consult with a qualified professional before using herbs during pregnancy. As with all medications, one should avoid taking any herb during the first trimester and use only minimal amounts for short periods of time thereafter, and then only when needed. [indiahomeclub;2008]

Many midwife and medical doctor using herbs in their practice with pregnant women for many years and found them to be helpful in treating many of the symptoms during those nine months of growing our

babies including nausea, insomnia, yeast infections, varicose veins, and hemorrhoids. They can even tone your uterus for labor. [Romm,2012] Pregnant women commonly experience minor symptoms for which natural remedies can actually be gentler and safer than pharmaceuticals many of which lack proof of safety in pregnancy or are known to be harmful. Overall, most herbs that are traditionally used to support pregnancy are safe for use in moderation. There have been almost no reports of adverse outcomes in pregnant women, and when they have occurred, it has been from using herbs that are not considered safe in pregnancy, or from products that have been tainted with unsafe herbs or even pharmaceutical additives – which has mostly been a problem with imported products from China and India. The safest approach is to avoid using herbs during the first trimester of pregnancy unless necessary (for example, ginger for treating morning sickness)

Herbal Products in Paediatrics

Because women make up the largest percentage of herbal users, it is not unexpected that they also administer herbal remedies to their children. Use of herbal medicines in preoperative patients has sparked great interest because of the possibility that such therapies may alter immune response, retard wound healing or interfere with drugs or coagulation parameters: relatively little is known about the incidence of herbal use specifically in the paediatric surgical population.

First of all, we must distinguish between neonates and children. In the first case, newborns could be

exposed to herbal products both indirectly (during the period of lactation) and directly.

How herbs may affect lactation in breastfeeding women has not been fully explored. The excretion of herbs into breast milk is a concern, as many herbs have lipophilic chemicals that may concentrate in breast milk and be transferred to the newborn. [Cuzzolin;2009]

In paediatric patients herbal products are used to promote health, to prevent illness and to treat acute but overall chronic, recurrent or incurable conditions such as asthma, atopic dermatitis, allergic rhinitis, cystic fibrosis, inflammatory bowel disease, rheumatoid arthritis or cancer.

Most herbal products have not been subjected to rigorous clinical trials, and there remains a dearth of knowledge concerning how children are affected by these substances. [Tomassoni;2001]

Paediatric subjects are physiologically more vulnerable to certain adverse effects of herbs than adults. For example, some herbs such as Senna and Aloe are known cathartics and some herbal teas contain powerful diuretic compounds: these actions may cause dehydration and electrolyte disturbances quickly in an infant or young child. Moreover, some subpopulations are more susceptible to certain adverse effects of herbs than other children. Subjects with allergies may be at increased risk, since the allergic potential of some plants commonly used in children that could cause contact dermatitis, rhinitis, conjunctivitis and wheezing is well known.

Safety Issues in infants and children taking herbal products

Monitoring the safety of medicine use in children is of paramount importance since, during the clinical development of medicines, only limited data on this aspect are generated through clinical trials. Risk factors that predispose children to develop an adverse reaction to a medicine can be physiological, indirect or iatrogenic. [WHO;2007]

Physiological causes for increased risks are because neonates and infants with the greatest physiological differences from adults; and also includes continuous changes of medicine dispositional parameters during maturation in all age classes.

Indirect causes for increased risks include greater prevalence of polypharmacotherapy, e.g. in the neonatal intensive care unit; greater length of hospital stay, e.g. children with congenital or chronic diseases; critically ill children, e.g. those who have neoplastic diseases.

Iatrogenic causes for increased risk include use of unlicensed and off-label medicines with very little information regarding appropriate dose, e.g. medicines used in orphan diseases such as cystic fibrosis; insufficient number of well-trained health-care professionals to treat seriously ill children.

Discussion

In several parts of the world, particularly in developing countries access to herbal medicines is largely unrestricted. In contrast to prescription and newer over the counter medications, herbal products are usually marketed without the benefit of clinical trials to demonstrate either efficacy or

safety.[Broussard;2010] Besides, manufacturers and purveyors of herbal medicines usually offer broad range of therapeutic claims which constitute powerful temptations for consumers. Indeed, few studies are available on the safety of herbs for pregnant women Interactions between herbs and conventional prescriptions should evolve serious concerns among pregnant women and the general public as some herbs may amplify the effects of anticoagulants while some, including common fruits, interfere with Cytochrome P450 enzyme systems which are critical to drug metabolism. Garlic is considered to be non toxic as a food additive, but in large quantities, there are concerns that it may act as an abortifacient calling for avoidance of medicinal doses in pregnancy.[Conover;2003] A study in rats had found an association between prenatal exposure to Ginger and increased fetal loss, increased fetal weight and bone maturation.[Wilkinson;2000] While another study on 27 women at 11 weeks gestation taking 1g ginger daily reported two abortion.[Fischer-Rasmussen;1990] Ginger is known to cause increased uterine activity and its action as a thromboxane synthetase inhibitor could affect testosterone receptor binding warranting cautious use and possibly avoiding doses above 1g per day during pregnancy.[Cuzzolin;2009]

The influence of mothers, peers, radio and television adverts, community societies and traditional healers were found to be significant in disseminating information on the use of herbal medicines. Although herbs have promising potential and are being increasingly used, many of them are untested

and their use is not monitored. As a result, knowledge of their side effect is limited. To promote phytomedicines as a source of healthcare, efforts must be made to promote its rational use.[Shirwaikar;2009]

Table.1. Reported Herbs causing severe adverse drug reactions (ADRs) in newborns after maternal herbal consumption during pregnancy and/or lactation.

Herbs	ADRs
Blue cohosh	Myocardial infarction, congestive heart failure
Blue and black cohosh	Seizures, kidney damage, respiratory problems
Blue cohosh	Seizures, encephalopathy, renal failure
Chamomile	Asphyxia
Ginseng	Neonatal androgenization
Pyrrolizidine alkaloids	Fatal liver injury
<i>Montanoa tomentosa</i>	Cardiorespiratory depression
Herbal tonic	Alcohol syndrome
<i>Tripterygium wilfordii</i>	Occipital meningoencephalocele, cerebellar agenesis

Conclusions

Use of herbal medicine among pregnant women is high. Clinicians and caregivers should have knowledge of the herbs commonly used by pregnant women and the potentials for toxicity. Attention should be given to enlightenment of pregnant women and the community on the dangers of herbal

drug use during pregnancy. It also unveils an association between herbal medicine use and illiteracy, low socioeconomic status and self

Table.2. Case report of adverse drug reactions (ADRs) in infants and children taking herbal products

Reference	Herbs	Subject	ADRs
Korkmaz et al.; 2000	Vinegar	Neonate	Burns
Koopman; 1937	<i>Chelidonium majus</i>	4-year-old child	Fatal colitis
Horowitz et al.; 1993	Jin Bu Huan	3 small children	Bradycardia, respiratory depression
Garty; 1993	Garlic	6-month-old infant	Burns
Canduela et al.; 1995	Garlic	6-year-old child	Necrotic ulcers
Bakerink et al.; 1996	Mint tea (pennyroyal oil)	2 infants	Multiple organ failure
Ernst; 2000	Asafetida gum	5-week-old infant	Methemoglobinemia
Steenkamp et al.; 2000	Pyrrrolizidine alkaloids	20 children	Hepatic veno-occlusive diseases
Bagheri et al.; 1998	Valerian	13-year-old child	Fulminant liver failure
Darben et al.; 1998	Eucalyptus oil	6-year-old child	Systemic intoxication

medication with orthodox drugs. Female formal education, health education as well as economic empowerment will help ensure women enlightenment and ability to appreciate the effects of drugs on the fetus, as well as afford appropriate drugs. Community mobilization is needed to control advertisements and ensure that information on the

risks and safety of herbal medicines to the fetus and mother in pregnancy are included in the package. There is also a need for health care providers to take adequate drug history and counsel pregnant women on possible dangers of herbal medicine use. Regulatory agencies may also need to strengthen regulations relating to licensing and use of herbal medicines in pregnancy in our environment. It is concluded that adverse effects of herbal medicines as well as their interactions with other prescription drugs should be known to the consumers and physicians. Herbal remedies under conventional therapy are known to show many benefits to humans, which is true but one should be fully familiar with their side effects at normal and large doses. One should also consider other herbal products for the possible risks while using in cure and treatments.

References

- Shirwaikar A, Verma R, Lobo R, Shirwaikar A, Phytotherapy-Safety Aspects; *Natural Product Radiance*, 2009;8(1), 55-63.
- Bagheri H, Brou`e P, Lacroix I, Larrey D, Olives JP, Vaysse P, Ghisolfi J, Montastruc JL; *Therapie* 53:77, (1998).
- Bakerink JA, Gospe SM, Dimand RJ, Eldridge MW "Multiple organ failure after ingestion of pennyroyal oil from herbal tea in two infants."; *Pediatrics* 98:944, (1996).
- Boivin, J, Schmidt, L, Use of complementary and alternative medicines associated with a 30% lower ongoing pregnancy/live birth rate during 12 months of fertility treatment. *Human Reproduction*, 2009; 21 (7):1626–1631.

- Born D; Barron ML, Herb use in pregnancy: what nurses should know. *MCN Am J Matern Child Nurs.*, 2005; 30 (3): 201-206.
- Broussard CS, Louik C, Honein MA, Mitchell AA, "Herbal use before and during pregnancy," *American Journal of Obstetrics & Gynecology*, 2010:202(5), 443-443.
- Canduela V, Mongil I, Carrascosa M, Docio S, Cagisgas P "Garlic: Always good for Health?" *Br J Dermatol* 132:161, (1995).
- Conover EA. Herbal Agents and Over the Counter Medications in Pregnancy: Best Practice & Research. *Clin Endocr Met*, 2003; 17 (2) : 237 –251.
- Marcus DM and Snodgrass WR, Do no harm: avoidance of herbal medicines during pregnancy, *Obstetrics & Gynecology*, vol. 105, no. 5, part 1; 2005; pp. 1119–1122.
- Darben T, Cominos B, Lee CT "Topical eucalyptus oil poisoning" *Australasian J Dermatol* 39:265, (1998).
- Dugoua J J, Mills E, Perri D, Koren G. Safety and Efficacy of Ginkgo (Ginkgo Biloba) during Pregnancy and Lactation. *Can J Clinical Pharmacology*, 2006; 13: 277-84.
- Elvin-Lewis, M., "Should we be concerned about herbal remedies". *Journal of Ethnopharmacology*, 2001; 75 (2–3): 141–164.
- Ernst E, Possible Interactions between Synthetic and Herbal Medicinal Products, *Perfusion*, 2000, 13, 4-15.
- Ernst E., "Herbal medicines: balancing benefits and risks". *Novartis Found. Symp.* Novartis Foundation; Symposia, 2007; 282: 154–67; discussion 167–72, 212–8.
- Fischer-Rasmussen W, Kjaer SK, Dahl C, Asping U. Ginger Treatment of Hyperemesis Gravidarum.; *European Journal of Gynaecology and Reproductive Biology*, 1990; 38: 19 – 24.
- Garty B "Garlic burns" *Pediatrics* 91:658, (1993).
- Horowitz RS, Gomez H, Moore LL, Fulton B, Feldhaus K, Brent J, Stermitz FR, Beck JJ, Alessi JR, De Smet PAGM (1993) *Mor Mortal Wkly Rep* 42:633 <http://ods.od.nih.gov/factsheets/BotanicalBackground-Pf.asp>; National Institutes of Health Office of Dietary Supplements. *Botanical Dietary Supplements: Background Information*. Dietary Supplement Fact Sheet (Oct. 30, 2008). <http://avivaromm.com/5-safe-herbs-for-a-more-comfortable-pregnancy-and-better-birth>; *5 Safe Herbs for a More Comfortable Pregnancy and Better Birth*; Aviva Romm (October 2, 2012). http://www.gaiagarden.com/articles/healthnotes/hn_herbtavoidduringpregnancy.php; *Herbs to avoid during pregnancy*; Gaia Garden website (2008). <http://www.herbalgram.com/herbalgram/product.com/>; Harvard study estimates consumers spend \$5.1billion on herbal products?, Blumenthal M., *Herbalgram*, 1999; 45, 68. http://www.indiahomeclub.com/safe_use_of_herbs/herbs_and_pregnancy.html; *Live Earth India home Club* (2008). <http://www.mayoclinic.org/healthy-living/nutrition-and-healthy-eating/in-depth/herbal-supplements/art-20046714>; Herbal supplements: What to know before you buy *By Mayo Clinic Staff* (2014). <http://www.plantphysiol.org>; Medicinal Plants and Phytomedicines. Linking Plant Biochemistry and Physiology to Human Health; Donald P. Briskin, *Plant Physiology*, October 2000, Vol. 124, pp. 507–514. http://www.who.int/hpr/NPH/docs/declaration_almaata.pdf , WHO's International

- Conference on Primary Health Care, Alma-Ata, USSR. 1978; 08 november 2009.
- Sajwan KCP, "Revitalizing Indian systems of herbal medicine by the National Medicinal Plants Board through institutional networking and capacity building". *Current Science*, 2007; 93 (6): 797–806.
- Ko RJ, Adulterants in Asian Patent Medicines; *N Eng J Med*, 1998; 399:847.
- Koopman H "Chelidonium majus" Vergiftungsf lle 8:93; (1937).
- Korkmaz A, Sahiner U, Yurdakok M "Pediatric Hospital Medicine: Textbook of Inpatient Management"; *Pediatr Dermatol* 17:34, (2000).
- Korver O, Functional foods: the food industry and functional foods: some European perspectives. In T Shibamoto, J Terao, T Osawa, eds, *Functional Foods for Disease Prevention:II. Medicinal Plants and Other Foods*. American Chemical Society, Washington, DC, 1998; 22–25.
- Laura Cuzzolin and Giuseppina Benoni Safety Issues of Phytomedicines in Pregnancy and Paediatrics K.G. Ramawat (ed.), *Herbal Drugs: Ethnomedicine to Modern Medicine*, Springer-Verlag Berlin Heidelberg, 2009; 381-396.
- Lin, Shih-Hua; Yang, SS; Chau, T; Halperin, ML, "An unusual cause of hypokalemic paralysis: chronic licorice ingestion". *Am J Med Sci* , 2003; 325 (3): 153–6.
- Lynch, Christopher R.; Folkers, ME; Hutson, WR, Fulminant hepatic failure associated with the use of black cohosh: a case report. *Liver Transpl.*, 2006; 12 (6): 989–992.
- Parson BJ, Dobbin M, Tibbals J (1997) *Aust N Z J Publ Health* 21:297
- Pinn G, "Adverse effects associated with herbal medicine". *Aust Fam Physician.*, 2001; 30 (11):1070–5.
- R.N. Okigbo and E.C. Mmeka, An Appraisal Of Phytomedicine In Africa Kmitl; *Sci. Tech. J.* Vol. 6 No. 2, Jul. - Dec. 2006; pp. 83-94.
- Seth SD, Sharma B. "Medicinal plants of India"; *Indian J. Medical. Research.*, 2004;20:9–11.
- Steenkamp V, Stewart MJ, Zuckerman M "Clinical and analytical aspects of pyrrolizidine poisoning caused by South African traditional medicines." *Ther Drug Monit* 22:302, (2000).
- Tomassoni AJ, Simone K. Herbal medicines for children: an illusion of safety? *Curr Opin Pediatr*, 2001 Apr;13(2):162-9.
- Tsui B, Dennehy C, Tsourounis C. A Survey of Dietary Supplement Use During Pregnancy at an Academic Medical Center. *American J Obstetrics Gynaecology*, 2001; 185: 433–437.
- Vickers AJ., "Which botanicals or other unconventional anticancer agents should we take to clinical trial?"; *J Soc Integr Oncology*, 2007; 5 (3): 125–9.
- WHO, Legal status of Traditional Medicines and complementary/Alternative Medicine: A worldwide review. WHO publishing 1, 2001.
- Wilkinson J M. Effect of Ginger Tea on the Fetal Development of Sprague-Dawley Rates. *Reproductive Toxicology*, 2000; 160: 3141 – 3143.
- World Health Organization, *Promoting safety of medicines for children*; ISBN 978-92-4-156343-7, (2007).