SAFETY AND EFFICACY OF GINKGO (GINKGO BILOBA) DURING PREGNANCY AND LACTATION

Jean-Jacques Dugoua[1,2], Edward Mills[3], Daniel Perri[4], Gideon Koren[2,4]

[1]Department of Clinical Epidemiology, Canadian College of Naturopathic Medicine, [2]Motherisk Program, Hospital for Sick Children, [3]Department of Clinical Epidemiology, McMaster University, [4]Department of Clinical Pharmacology and Toxicology, University of Toronto

Corresponding Author: *jeanjacques.dugoua@utoronto.ca*

ABSTRACT

Background
There is a lack of basic knowledge on the part of both clinicians and patients as to the indications for use and safety of herbal medicines used in pregnancy and lactation. This is one article in a series that systematically reviews the evidence for commonly used herbs during pregnancy and lactation.

Objectives
To systematically review the literature for evidence on the use, safety, and pharmacology of ginkgo focusing on issues pertaining to pregnancy and lactation.

Methods
We searched 7 electronic databases and compiled data according to the grade of evidence found.

Results
There is some very weak scientific evidence from animal and *in vitro* studies that ginkgo leaf has anti-platelet activity, which may be of concern during labour as ginkgo use could prolong bleeding time. Low-level evidence based on expert opinion shows that ginkgo leaf may be an emmenagogue and have hormonal properties. The safety of ginkgo leaf during lactation is unknown. Patients and clinicians should be aware of past reports of ginkgo products being adulterated with colchicine.

Conclusions
Ginkgo should be used with caution during pregnancy, particularly around labour where its anti-platelet properties could prolong bleeding time. During lactation the safety of ginkgo leaf is unknown and should be avoided until high quality human studies are conducted to prove its safety.

Key Words: *Ginkgo, ginkgo biloba, pregnancy, lactation, breastfeeding, systematic review*

The ginkgo biloba tree is the world's oldest living tree – its species can be dated back to over 250 million years.

It is believed that they once occurred naturally in Asia, Europe and America but they disappeared from America about 7 million years ago and from Europe about 3 million years ago. It wasn't until the eighteenth century that ginkgo was cultivated again in Europe and North America.

It is a very hearty plant and, in fact, in the spring following the atomic bombing of Hiroshima, an old ginkgo tree was the only flora to resprout. The use of Ginkgo for medicinal uses can be traced back to the oldest Chinese materia medica – about 2800 BC. Traditional Chinese medicine has used the ginkgo leaves for brain disorders, circulatory disorders, respiratory diseases such as asthma, urinary tract disorders, and as an antiparasitic.

Modern research on ginkgo and the physiologic effects of its constituents began in Japan in the 1920s with its cardiovascular effects documented as early as 1965, and the first standardized extract available on the market in 1975.[1]

Ginkgo leaf extracts are now among the leading prescription medicines in both Germany and France, where they account for 1 and 1.5%, respectively, of total prescription sales. Over the last few years ginkgo has also become the top selling herbal medicine in the United States.[2] It is used to treat mild dementia, peripheral vascular disease, and tinnitus. It is also commonly used as a memory enhancer by healthy patients. Although its popularity in women's health is for stroke and dementia in the elderly, it is used by women of childbearing age for memory boosting, asthma, mountain sickness, varicose veins, or sometimes for idiopathic cyclic edema.[3] More recently, it has had a growing popularity in the treatment of sexual dysfunction secondary to the use of selective serotonin reuptake inhibitors.[4] Young women with connective tissue disorders also use it and, the World Health Organization has recommended the use of ginkgo for Raynaud's disease.[5]

Although women of reproductive age use ginkgo for a variety of indications, there is disagreement among scientists, clinicians, herbalists, and consumers with regards to the effectiveness and safety of ginkgo. Furthermore, there is debate regarding the safety of ginkgo during pregnancy or breastfeeding. This paper addresses the issues of efficacy of ginkgo for a variety of indications as well as the safety of gingko use by pregnant or breastfeeding women by reporting the results of a systematic review of the literature on ginkgo biloba's clinical use.

METHODS

The following databases were searched from inception to June 2005: AMED, CINAHL, Cochrane CENTRAL, Cochrane Library, MedLine, Natural Database, and Natural Standard. The common name and Latin name of the herb were used as keywords along with "pregnancy", "lactation", and "breastfeeding". In the case of a well-known active constituent of the herb, this term was also used in the search for its safety during pregnancy and lactation. In addition, the Complete German Commission E Monographs by the American Botanical Council were also searched.

Each relevant journal article was collected and referenced in a database. The nature of the findings and the grade of evidence were then abstracted and compiled in a final report. The grade of evidence for indications was evaluated as displayed in Table 1. Evidence of harm was rated as displayed in Table 2

RESULTS

Synonyms/ Common Names/ Related Substances[6]
Adiantifolia, bai guo ye, fossil tree, *Ginkgo folium*, ginkgo leaf, ginkyo, Japanese silver apricot, kew tree, maidenhair tree, salisburia, *Salisburia adiantifolia*, yinhsing, baiguo.

Indications for Use

Leaf

	Grade
Intermittent claudication – Peripheral vascular disease[11-13]	A
Dementia (Alzheimer's disease and other)[8,14,15]	A
Cerebrovascular insufficiency[16-18]	A
Tinnitus[19,20]	A
Age-associated memory impairment[21-23]	B1
Memory enhancement in healthy individuals[24-26]	B1
Altitude sickness[27]	B1
Vertigo[17]	B1
Premenstrual syndrome (PMS)[28]	B1
Macular degeneration[29]	B2
Erectile dysfunction[30-33]	C
Antidepressant-induced sexual dysfunction[34]	C
Chemotherapy adjunct[35,36]	C
Multiple sclerosis[37]	D
Light-induced retinal damage[38]	E

Seed

	Grade
Cough, expectorant, asthma, bronchitis[6]	E
Skin sores and scabies (topical)[6]	E

Safety of Consumption during Pregnancy

Leaf

	Level
Unsafe when adulterated with colchicine[39]	1c
Antiplatelet[40,41]	3
Emmenagogue[42]	4
Hormonal changes[42]	4

Roasted Seed

Possibly safe if taken as food[10]	4

Raw Seed

Possibly unsafe[9]	4

A case series reported the presence of colchicine in the placental blood of pregnant women having taken ginkgo.[39] The source of colchicine was traced back to the consumption of a commercially available *Ginkgo biloba* product that contained colchicine.[39] Given that colchicine is not a common constituent of gingko, the observed finding is most likely due to an adulteration of a ginkgo product by a herb containing colchicine. The antiplatelet properties of ginkgo leaf may prolong bleeding during delivery.[40,41]

A herb toxicology and drug interaction compendium reported that ginkgo leaf is an emmenagogue and can cause hormonal changes.[42] Ginkgo leaf was not reported in the evidence-based medicine literature as being an emmenagogue or causing hormonal changes, nor was it reported as being contraindicated in pregnancy. A toxicology compendium reported that roasted ginkgo seeds may be potentially safe if eaten as a food during pregnancy.[10] A toxicology compendium reported that raw ginkgo seeds (non-roasted) may be a concern in pregnancy if they are used medicinally.[9] Roasted and raw ginkgo seed were not reported in the evidence-based medicine literature as being either safe or contraindicated in pregnancy.

Safety of Consumption during Lactation

Leaf

	Level
Unknown	5

Roasted seed

Possibly safe if taken as food[10]	4

Raw Seed

Possibly unsafe[9]	4

Ginkgo leaf was not reported in the evidence-based medicine literature as being either safe or contraindicated during lactation. A toxicology compendium reported that roasted ginkgo seeds may be potentially safe if eaten as a food during lactation.[10] A toxicology compendium reported that raw ginkgo seeds (non-roasted) may be a concern in lactation if they are used medicinally.[9] Roasted and raw ginkgo seed were not reported in the evidence-based medicine literature as being either safe or contraindicated in lactation.

Parts Used

Leaf, seed[6].

Constituents

- Leaf**:** Flavonoids[7] (rutin, isorhamnetine, quercetin, kaempferol, proanthocyanidins)
- terpenoids[8] (ginkgolides A, B, C, M and J, bilobalide)
- organic acids[6]
- Seed: Cyanogenic glycosides[9]
- ginkgotoxin[9,10].

Toxicology

Leaf

Crude extracts of ginkgo leaf may contain ginkgolic acids, which are suspected to have cytotoxic, allergenic, mutagenic and carcinogenic properties.[43,44] The LD_{50} in mice is 7,725mg.[45]

Seed

Ginkgotoxin, found in ginkgo seed, may cause seizures, loss of consciousness and death.[9,10]

Pharmacology

Leaf

Ginkgo increases cerebral and peripheral blood circulation.[46,47] Ginkgo reduces vascular permeability, causes vascular contraction, improves venous tone, inhibits phosphodiesterase type 4 (PDE4), relaxes vascular smooth muscle via a nitric oxide pathway, and improves blood flow to the corpus cavernosum of the penis.[30,46-48] Ginkgo reduces platelet aggregation by competitively binding platelet activating factor (PAF) and by inhibiting the formation of platelet thromboxane A2.[38,40,41,49]

The ginkgo flavonoids have antioxidant and free radical scavenging properties.[8,15,38,40,50] Partially due to its antioxidant activity, ginkgo inhibits the toxicity and cell death induced by beta-amyloid plaques in Alzheimer's disease.[51] Ginkgo decreases systolic and diastolic blood pressure, increases fasting plasma insulin and C-peptide, decreases cortisol secretion and decreases the secretion of corticotropic releasing hormone (CRH).[40,52,53]

Ginkgo may inhibit cytochrome P450 3A4, indue cytochrome P450 3A5, and mildly inhibit cytochrome P450 1A2 and 2D6.[6,54,55]

Seed

The cyanogenic glycosides have antibacterial and antifungal effects.[6,9]

Drug Interactions

Leaf

- Anticoagulant/Antiplatelet Drugs[38,40,41]
- Fluoxetine[56]
- Buspirone[56]
- St. John's wort[56]
- Melatonin[56]
- Insulin[40]
- Monoamine oxidase inhibitors (MAOIs)[57-59]
- Seizure threshold lowering drugs[60,61]
- Thiazide diuretics[62]
- Trazodone[55]
- Warfarin[63]
- Drugs metabolized by cytochrome P4503A4, P450 3A5, P450 1A2 and P450 2D6 enzymes.[6,54,55]

DISCUSSION

Most of the beneficial therapeutic effects of *Ginkgo biloba* appear to be derived from the leaf. There is very strong evidence for the therapeutic use of ginkgo for intermittent claudication (peripheral vascular disease), dementia (including Alzheimer's disease), cerebrovascular insufficiency, and tinnitus. There is strong evidence for use in age-associated memory impairment, memory enhancement in healthy individuals, altitude sickness, vertigo, and premenstrual syndrome (PMS). Lastly, there is good evidence for use in macular degeneration.

During pregnancy, the main concern with using ginkgo leaf revolves around its antiplatelet activity as documented in animal studies. Although based on *in vitro* evidence, there is a valid concern that ginkgo use could prolong bleeding during delivery. Based on this finding, it would be prudent to discontinue use of ginkgo weeks prior to delivery. In addition, patients and clinicians should be aware of manufacturers employing Good Manufacturing Practices (GMP) when choosing ginkgo products as a case series reported the adulteration of ginkgo with colchicine.

During lactation, ginkgo should be used with caution, as there is no documentation in the scientific literature related to its safety during lactation. With respect to ginkgo seed, theoretical evidence suggests that raw ginkgo seed should be avoided during pregnancy and lactation, while roasted ginkgo seed may possibly be safe if eaten in food amounts.

While traditional and common use has not indicated any substantive risks of taking this herb during pregnancy and lactation, clearly more rigorous and well-controlled research is needed in this area. Clinicians and patients should also be concerned about the potential for interactions that may occur between ginkgo and numerous prescription medications, particularly anticoagulant and antiplatelet drugs. This issue has greater significance when the possibility for increased exposure or toxicity to the developing fetus might result from altered drug metabolism due to interaction.

TABLE 1 Grades for evidence for efficacy

GRADE	EVIDENCE
A	**VERY STRONG SCIENTIFIC EVIDENCE** Statistically significant evidence of benefit from one or more systematic reviews/ meta-analysis.
B1	**STRONG SCIENTIFIC EVIDENCE** Statistically significant evidence of benefit from one or more properly conducted random control trials (RCTs).
B2	**GOOD SCIENTIFIC EVIDENCE** Statistically significant evidence of benefit from one or more RCTs. The RCTs, however, are either of small sample size OR have discrepancies in their methodologies.
C	**FAIR SCIENTIFIC EVIDENCE** Statistically significant evidence of benefit from one or more cohort studies OR outcome studies.
D	**WEAK SCIENTIFIC EVIDENCE** Evidence from case series.
E	**INDIRECT AND/OR CLINICAL EVIDENCE** Evidence from case reports OR expert opinion OR laboratory studies.
F	**HISTORICAL OR TRADITIONAL EVIDENCE** Historical or traditional use by medical professionals, herbalists, scientists, or aboriginal groups.

TABLE 2 Levels for evidence for harm

LEVEL	EVIDENCE
1a	**STRONG SCIENTIFIC EVIDENCE** Statistically significant evidence from one or more systematic reviews or RCTs.
1b	**GOOD SCIENTIFIC EVIDENCE** Statistically significant evidence from one or more cohort studies OR control study.
1c	**WEAK SCIENTIFIC EVIDENCE** Evidence from one or more case series.
2	**VERY WEAK SCIENTIFIC EVIDENCE** Evidence based on case reports.
3	***IN VITRO* SCIENTIFIC EVIDENCE** Evidence based on scientific studies conducted on animals, insects or microorganisms OR laboratory studies on human cells.
4	**INDIRECT EVIDENCE** Evidence based on scientific theory OR expert opinion.
5	**UNKNOWN** No available information.

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