

Fetal safety of medicinal herbs and food ingredients during pregnancy: Recommendations from traditional Korean medicine based on expert opinions

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Objectives: This study aimed to establish and provide reliable information for general public, based on expert consensus, on the risks of misuse of medicinal herbs for food and pure food ingredients for the fetus during pregnancy.

Methods: A panelist of seven traditional Korean medicine (TKM) gynecologists responded to a questionnaire summarizing the fetal safety literature for twenty-five medicinal herbs for food and pure food ingredients derived from medicated diet (藥膳, Yaksun) recipes during three online Delphi rounds anonymously.

Results: Ginkgonis Semen (Ginkgo nut), Illici Veri Fructus (Star anise), lavender, bitter melon, and parsley were agreed at the level 1 of “Do not consume”. These five ingredients were recognized as having significant risks both in the literature evidence and in expert opinion. Rosemary, Citri Unshius Pericarpium, Discoscorea Rhizoma, lemongrass, Schisandrae Fructus, Cassiae Semen, Foeniculi Fructus, Mori Fructus, Cinnamomi Cortex, and Astragali Radix were agreed at the level 2 of “consultation with TKM practitioner is required”.

Conclusion: Based on the consensus of a seven-member expert panel of TKM gynecologists, consumption of Ginkgonis Semen (Ginkgo nut), Illici Veri Fructus (Star anise), lavender, bitter melon, and parsley should be avoided by pregnant women. For Rosemary, Citri Unshius Pericarpium, Discoscorea Rhizoma, lemongrass, Schisandrae Fructus, Cassiae Semen, Foeniculi Fructus, Mori Fructus, Cinnamomi Cortex, and Astragali Radix, the level 2 advisory may be recommended to use with caution and to consult a TKM practitioner for advice on consumption, dose, and duration.

Key Words : Medicinal herbs for food, Pregnant women, Medicated diet, Delphi study, Korean traditional medicine

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Introduction

The number of medicinal herbs for food use, which can be institutionally marketed as both agricultural products and specialized medicinal herbs, is relatively high in Korea compared to China, Japan, and Taiwan and some of these medicinal herbs for food use in Korea are not allowed to be used as medicinal purpose in Japan. Experts in Korea have been calling for complementing the system to prevent these potential public risks from misuse¹⁾. On the other hand, the risks of misuse of medicinal herbs are not well known to the general public, who are often unaware of the dangers posed by the easy availability of medicinal herbs in the marketplace, both online and offline²⁾. A study using Naver DataLab service to analyze the search trends of health food consumers' online purchases of medicinal herbs reported that many medicinal herbs are purchased to drink boiled extract water or to use as an ingredient in ordinary food, and that the search volume increased with the trend cycle of a particular medicinal herb³⁾. On the other hand, demands for dietary supplements including medicinal herbs in Korea is growing steadily every year⁴⁾. A study that examined the food ingredients used in Korean medicated diet restaurants reported that ninety-six medicinal herbs for food use were used, including some that could be recognized as specialized medicinal herbs such as *Paeoniae Radix*, *Atractylodis Rhizoma Alba*, *Cervi Parvum Cornu*, *Acori Gramineus Rhizoma*, *Leonuri Herba*, and *Araliae Continentalis Radix*⁵⁾. This is considered to be owing to the fact that some people in Korea still

have a false perception that naturally grown and harvested agricultural products, whether they are used as medicinal herbs or not, are safe enough when even taken for a long period⁶⁾.

East Asian countries have a long history of public use of medicinal herbs in their daily life, and the line between medicinal herbs and foods has always been blurred from the beginning. Therefore, the research of medicinal herbs for food use has not solely been limited to therapeutic purpose. In Korea, dietary therapy (食治) using medicinal herbs for food use is known to begin to be practiced professionally in the Chosun Dynasty, and the ingredients including medicinal herbs used in medicated diets are recorded in farming books related to cultivation, gathering, and production, geographical map books related to major production areas, and food recipe books⁷⁾. According to a study that systematically reviewed the trends of medicated diets research in Korea, it was found that more research was conducted on food science value and productivity than on the efficacy of medicinal herbs, which was conducted by experts in traditional Korean medicine (TKM). In addition, the researchers' specialties were mainly focused on food nutrition and food science majors⁸⁾.

Moreover, in pregnant women who are carrying a fetus that is vulnerable to the potential hazards posed by these environments, the potential for adverse, even minor, effects on the fetus cannot be ruled out enough. However, it is not easy for pregnant women in Korea to access reliable safety information on medicinal herbs for food use. Therefore, we anticipated that a large number of pregnant women would likely make their

consumption decisions based on internet media such as searching portal websites, online communities, or unsubstantiated information from acquaintances⁹⁾. The fetal safety of herbs used abroad has been extensively reported at the literature review level, however the medicinal herbs for foods and pure food ingredients used in Korea are different from those used abroad. Therefore, it is necessary to set up a list of medicinal herbs for food and pure food ingredients and conduct research according to domestic environments^{10,11,12)}.

In this study, we created a Delphi questionnaire based on literature including previously reported clinical, animal experimental, and literature review studies, and conducted an expert consensus online Delphi study with seven TKM gynecologists working in pregnancy care practice setting. On the one hand, we aimed to secure the safety of unborn children who are vulnerable to this risk by preventing the potential risk of misuse of medicinal herbs for food. On the other hand, we aimed to help general public by providing relatively objective information on misconceptions about food ingredients that are often dismissed without any evidence. In the future, we would like to disclose this consensus information to the general public in the form of individual safety information for each herb or ingredient.

Methods

1. Collecting literatures and creating questionnaire form

We collected medicated diet and herbal tea recipes published on the popular internet web

portals including Naver (<http://www.naver.com/>), Baidu (<http://www.baidu.com/>), Google (<http://www.google.com/>) and YouTube (<http://www.youtube.com/>) to extract the list of medicinal herbs for food and pure food ingredients, and collected and analyzed the fetal safety literature on them. Due to the nature of medicated diets, we determined that recipes from ancient sources are not currently applicable in practice. Therefore, we used common portal websites for collecting recipes that seemed to be available today. Search terms such as “食疗” (diet therapy), “药膳” (medicated diet), and “药茶” (medicated tea) were used and recipes were mainly collected from videos on the medicated diet YouTube channel 侯老师说食疗, posts on the websites such as 解疑经验百科 (<https://mip.jiankangti.com/>), 360doc个人图书馆 (<http://www.360doc.com/>), and 百度百科 (<https://baike.baidu.com/>). The scope of the safety assessment was limited to the safety of fetal developmental abnormalities and miscarriage during pregnancy, however did not include maternal safety during pregnancy, safety during labor, or fetal safety during breastfeeding period. Among the candidate ingredients, a list of medicinal herbs for food and pure food ingredients deemed to have a high risk to the fetus was derived, and medicinal herbs that are not medicinal herbs also for food use based on the Food Standards and Standards Act in Korea was excluded. Fetal safety literatures until December 29th, 2021 were collected from Google Scholar (<http://scholar.google.com/>) and PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) databases using the following English search terms : each herbs and food name with scientific name, “pregnancy”,

“pregnant”, “fetus”, “fetal”, “safety”, and “toxicity”. Of the literature collected and reviewed, the final 86 articles were included as references in the questionnaire. After prior consultation with experts, including five TKM gynecologists, four levels of caution for pregnant women’s consumption of medicinal herbs for foods and pure food ingredients was derived, and these four levels were presented as options in a Delphi consensus questionnaire summarizing the fetal safety literature for each ingredient. In presenting the safety summaries of the literature papers by ingredients, we categorized ingredients by human clinical, animal experimental, and literature review studies.

2. Recruiting Delphi expert panels

We officially requested recommendations to the Society of Korean Medicine Obstetrics and Gynecology and received a list of twenty-one TKM gynecologists in pregnancy care setting including information of name, phone number, email address, gender, age, practice area, and affiliation. A final seven-member expert panel was selected based on considering diversity of practice setting (University hospital, general hospital, and clinic) and geography, professional recognition, and age distribution. The selected expert panels were individually informed of the purpose and methodology of this Delphi study and asked to agree to participate from a moderator. The Delphi consensus questionnaire was emailed to each panel and they were instructed by the moderator to select a rating level of caution for each ingredient, along with the reasons for their choices. The study protocol

including methodology for collecting expert information and disclosing consensus results was approved by the Institutional Review Board of the Korea Institute of Oriental Medicine (I-2210/010-002). The Institutional Review Board were responsible for supervising all aspects of the study.

3. Delphi process and consensus criteria

The Delphi research process was conducted exclusively online in three rounds from March 2nd to April 19th, 2023, and any disagreements in each Delphi round were resolved in the next round of consensus. The criteria for determining agreement and disagreement, which were established upon providing the questionnaire, were as follows, and were presented in the instructions for the initial distribution of the questionnaire: i) For each ingredient, consensus or agreement was defined as an intake caution rating selected by at least four of seven panels and differing by at least two points from the next highest frequency rating; ii) For each ingredient, disagreement was defined as the caution rating with the highest frequency less than 4 or differing between the most and next frequent ratings less than or equal to one. If the same item was disagreed in a similar distribution of response during two rounds of Delphi, the following revised criteria for third round was defined and distributed to the panels. If the third round of consensus resulted in a disagreement based on the initial judgement criteria, the moderator would simply determine the most frequent caution rating as agreed, however if two caution ratings were selected with equal frequency, a stricter level of

rating was selected as consensual.

The results of each Delphi round were shared anonymously with all panelists, including the reasons for their choices prior to the next Delphi round, and the consensus process was repeated on the same questionnaire with only the item that was not agreed upon. All expert opinions remained anonymous from the beginning of the Delphi consensus to the end of the study.

Results

1. Deriving ingestion caution levels

The ingestion caution levels were derived as follows: 1. Do not consume; 2. May be used with caution in dosage and duration after consultation with a TKM practitioner (required); 3. Self-consumption is possible, however consultation with a TKM practitioner is recommended; 4. Can be consumed without special caution. The ingestion caution levels, along with the evaluation notes provided to the panelists, are presented in Table 1.

2. Ingredients included in the Delphi questionnaire

In total, the literatures for twenty-five medicinal herbs for food and pure food ingredients were summarized and references were provided to the panelists along with the type of evidence. Fourteen ingredients had clinical research evidences, eight ingredients had no clinical research evidences however animal research evidences, and three ingredients had only literature review evidences in the Delphi questionnaire. The classification and list of medicinal herbs for food and pure food ingredients are presented in Table 2⁽¹³⁾. Clinical research evidence included three Cochrane systematic reviews, seven randomized controlled trials, and four prospective cohort studies, with the most clinically studied ingredients being coffee/green tea (caffeine), *Allii Bulbus* (garlic), *Zingiberis Rhizoma* (ginger), *Ginseng Radix*, and chamomile.

3. Delphi panelists and process

The panelists consisted of five professors from

Table 1. The Ingestion Caution Ratings and Evaluation Notes for Panelists

The ingestion caution ratings	Evaluation notes for panelists
1. Do not consume	Ingredients with this level are advised against consumption, and no medicated diet recipes using them are provided.
2. May be used with caution in dosage and duration after consultation with a TKM practitioner (required)	Please consider anticipated public reaction to this rating. If you anticipate such resistance, we recommend to select level 3 or 4. (Please consider the expected reaction in South Korea when it is suggested that pregnant women should consult a TKM doctor when consuming garlic, soy bean, or coffee.)
3. Self-consumption is possible, however consultation with a TKM practitioner is recommended	Please consider selecting this level if the risk of toxic side effects is low in both magnitude and probability. If the probability of occurrence is low, however the magnitude of risk is not insignificant, we recommend to select level 2.
4. Can be consumed without special caution	Only limited to amount of normal daily meal intake. If you are concerned about overconsumption for self-medication purposes, we do not recommend selecting this level.

Abbreviations: TKM, traditional Korean medicine

1st round														
No.	Ingredient name	Other name	Agreement/disagreement	P1	P2	P3	P4	P5	P6	P7	① Do not consume	② May be used with caution in dosage and duration after consultation with a traditional Korean medicine practitioner (required)	③ Self-consumption is possible, however consultation with a traditional Korean medicine practitioner is recommended	④ Can be consumed without special caution
2.1.1	Coffee/green tea		Agreement	③	③	③	②	④	②	③	0	2	4	1
2.1.2	Allii Bulbus	Garlic	Agreement	③	③	③	③	④	③	③	0	0	5	2
2.1.3	Zingiberis Rhizoma	Ginger	Agreement	④	③	③	④	④	③	③	0	1	4	2
2.1.4	Ginseng Radix		Agreement	②	②	②	③	③	②	②	0	2	5	0
2.1.5	Chamomile		2nd round	④	③	③	②	④	②	③	0	2	2	3
2.1.6	Astragal Radix		Agreement	②	②	②	③	③	③	③	1	4	2	0
2.1.7	Soybean		2nd round	③	④	③	③	④	③	③	0	0	4	3
2.1.8	Mori Fructus	Mulberry	2nd round	②	②	②	②	④	③	③	1	3	2	1
2.1.9	Foeniculi Fructus	Fennel seed	Agreement	②	②	②	②	③	③	③	1	5	1	0
2.1.10	Parsley		Agreement	③	①	④	②	③	③	③	4	1	1	1
2.1.11	Menthae Herba	Peppermint	2nd round	②	②	④	③	③	③	③	1	2	3	1
2.1.12	Ilicii Veri Fructus	Star anise	Agreement	①	①	③	③	③	③	③	4	2	1	0
2.1.13	Lavender		Agreement	①	①	③	②	③	③	③	4	1	2	0
2.1.14	Ginkgonis Semen	Ginkgo nut	2nd round	③	①	②	②	③	③	③	3	2	2	0
2.2.1	Cinnamomi Cortex	Cinnamon	2nd round	②	②	③	③	②	③	③	1	3	3	0
2.2.2	Rosemary		2nd round	②	②	③	②	④	③	③	1	3	2	1
2.2.3	Bitter gourd		Agreement	③	①	②	②	③	③	③	4	2	1	0
2.2.4	Cassiae Semen	Sicklepod	2nd round	②	②	③	③	④	③	③	1	2	2	2
2.2.5	Artemisiae Argyi Folium	Korean mugwort	Agreement	②	②	③	③	③	③	③	1	2	4	0
2.2.6	Citri Unshius Pericarpium	Tangerine peel	2nd round	②	②	②	②	④	③	③	1	3	2	1
2.2.7	Discorae Rhizoma	Chinese yam	2nd round	②	②	③	②	③	③	③	1	3	3	0
2.2.8	Lemongrass		2nd round	③	②	②	②	③	③	③	1	3	3	0
2.3.1	Schisandrae Fructus	Schisandra berry	2nd round	②	②	④	③	②	③	③	1	3	2	1
2.3.2	Crataegi Fructus	Hawthorn berry	2nd round	②	①	②	③	③	③	③	2	2	3	0
2.3.3	Lemon balm		Agreement	③	②	③	②	③	③	③	1	2	4	0

2nd round														
No.	Ingredient name	Other name	Agreement/disagreement	P1	P2	P3	P4	P5	P6	P7	① Do not consume	② May be used with caution in dosage and duration after consultation with a traditional Korean medicine practitioner (required)	③ Self-consumption is possible, however consultation with a traditional Korean medicine practitioner is recommended	④ Can be consumed without special caution
2.1.5	Chamomile		Agreement	④	③	④	③	④	④	④	0	0	2	5
2.1.7	Soybean		3rd round	③	④	③	③	④	③	③	0	0	3	4
2.1.8	Mori Fructus	Mulberry	Agreement	②	③	②	③	②	②	②	0	5	2	0
2.1.11	Menthae Herba	Peppermint	Agreement	③	③	③	③	③	③	③	0	0	7	0
2.1.14	Ginkgonis Semen	Ginkgo nut	Agreement	③	③	③	②	③	③	③	6	1	0	0
2.2.1	Cinnamomi Cortex	Cinnamon	Agreement	②	②	②	③	②	②	③	0	5	2	0
2.2.2	Rosemary		3rd round	②	②	③	③	②	②	③	1	3	3	0
2.2.4	Cassiae Semen	Sicklepod	3rd round	②	②	③	③	②	②	②	0	4	3	0
2.2.6	Citri Unshius Pericarpium	Tangerine peel	Agreement	②	②	②	③	②	②	②	0	6	1	0
2.2.7	Discorae Rhizoma	Chinese yam	Agreement	②	③	②	②	②	②	②	0	6	1	0
2.2.8	Lemongrass		Agreement	②	②	②	②	②	②	②	0	6	1	0
2.3.1	Schisandrae Fructus	Schisandra berry	Agreement	②	②	②	③	②	②	②	0	6	1	0
2.3.2	Crataegi Fructus	Hawthorn berry	Agreement	②	②	②	③	②	②	②	0	2	5	0

3rd round														
No.	Ingredient name	Other name	Agreement/disagreement	P1	P2	P3	P4	P5	P6	P7	① Do not consume	② May be used with caution in dosage and duration after consultation with a traditional Korean medicine practitioner (required)	③ Self-consumption is possible, however consultation with a traditional Korean medicine practitioner is recommended	④ Can be consumed without special caution
2.1.7	Soybean		Agreement	④	④	④	④	④	④	④	0	0	0	7
2.2.2	Rosemary		Agreement	②	②	②	②	②	②	②	0	7	0	0
2.2.4	Cassiae Semen	Sicklepod	Agreement	②	②	②	②	②	②	②	0	6	1	0

Fig 1. Records of each Delphi expert consensus process and distribution of panelist responses. The circled numbers in each panel represent the ratings, and a bold, underlined number means it was selected and agreed upon with that frequency of response.

TKM university hospital, one specialist from a TKM general hospital, and one specialist from a TKM clinic. The expert panelists' practice locations were relatively evenly distributed across the country, including Seoul, Gyeonggi-do, Chungcheongbuk-do, Daejeon, Jeollanam-do, Gyeongsangbuk-do, and the average age of the

panelists was 48.7 years, with a 5:2 male-to-female ratio. The expert Delphi consensus process took place online in three rounds from March 2nd to April 19th, 2023.

4. Expert Delphi consensus results

In the first round of Delphi, 12 of the 25

Summary			Agreement/disagreement							Consensus results			
No.	Ingredient name	Other name	P1	P2	P3	P4	P5	P6	P7	① Do not consume	② May be used with caution in dosage and duration after consultation with a traditional Korean medicine practitioner (required)	③ Self-consumption is possible, however consultation with a traditional Korean medicine practitioner is recommended	④ Can be consumed without special caution
2.1.1.	Coffe/green tea		①	①	①	①	①	①	①	0	2	4	1
2.1.2.	Allii Bulbus	Garlic	②	②	②	②	②	②	②	0	0	5	2
2.1.3.	Zingiberis Rhizoma	Ginger	④	④	④	④	④	④	④	0	1	4	2
2.1.4.	Ginseng Radix		②	②	②	②	②	②	②	0	2	5	0
2.1.5.	Chamomile		④	④	④	④	④	④	④	0	0	2	5
2.1.6.	Astragali Radix		②	②	②	②	②	②	②	1	4	2	0
2.1.7.	Soybean		④	④	④	④	④	④	④	0	0	0	7
2.1.8.	Mori Fructus	Mulberry	②	②	②	②	②	②	②	0	5	2	0
2.1.9.	Foeniculi Fructus	Fennel seed	②	②	②	②	②	②	②	1	5	1	0
2.1.10.	Parsley		③	③	③	③	③	③	③	4	1	1	1
2.1.11.	Menthae Herba	Peppermint	③	③	③	③	③	③	③	0	0	7	0
2.1.12.	Illici Veri Fructus	Star anise	③	③	③	③	③	③	③	4	2	1	0
2.1.13.	Lavender		③	③	③	③	③	③	③	4	1	2	0
2.1.14.	Ginkgonis Semen	Ginkgo nut	③	③	③	③	③	③	③	6	1	0	0
2.2.1.	Cinnamomi Cortex	Cinnamon	②	②	②	②	②	②	②	0	5	2	0
2.2.2.	Rosemary		②	②	②	②	②	②	②	0	7	0	0
2.2.3.	Bitter gourd		①	①	①	①	①	①	①	4	2	1	0
2.2.4.	Cassiae Semen	Sicklepod	②	②	②	②	②	②	②	0	6	1	0
2.2.5.	Artemisiae Argyi Folium	Korean mugwort	②	②	②	②	②	②	②	1	2	4	0
2.2.6.	Citri Unshius Pericarpium	Tangerine peel	②	②	②	②	②	②	②	0	6	1	0
2.2.7.	Discoreae Rhizoma	Chinese yam	②	②	②	②	②	②	②	0	6	1	0
2.2.8.	Lemongrass		②	②	②	②	②	②	②	0	6	1	0
2.3.1.	Schisandrae Fructus	Schisandra berry	②	②	②	②	②	②	②	0	6	1	0
2.3.2.	Crataegi Fructus	Hawthorn berry	③	③	③	③	③	③	③	0	2	5	0
2.3.3.	Lemon balm		③	③	③	③	③	③	③	1	2	4	0

Fig 2. Summary of final consensus results and distribution of panelists responses. The circled numbers in each panel represent the ratings, and a bold, underlined number means it was selected and agreed upon with that frequency of response.

ingredients resulted in consensus, and the second round of Delphi was conducted for the 13 disagreed ingredients that did not meet the consensus threshold, resulting in additional consensus for 10 ingredients. The remaining three ingredients—soybean, rosemary, and Cassiae Semen—reached consensus in the third round of Delphi (Figure 1,2). Consequently, a consensus was reached for 5 ingredients at level 1 advisory (Do not consume), 10 ingredients at level 2 advisory (May be used with caution in dosage

and duration after consultation with a TKM practitioner (required)), 8 ingredients at level 3 advisory (Self-consumption is possible, however consultation with a TKM practitioner is recommended), and 2 ingredients at level 4 advisory (Can be consumed without special caution) (Table 3).

Analysis of opinions gathered during the three rounds of expert consensus revealed that panelists seemed to have perceived greater risk for ingredients included in the questionnaire when

Table 2. The list of medicinal herbs for food and pure food ingredients

Classification	Name of ingredient
Medicinal herbs for food	Allii Bulbus (garlic), Zingiberis Rhizoma (ginger), Ginseng radix, Astragali Radix, Mori Fructus (Mulberry), Foeniculi Fructus (fennel seed), Menthae Herba (peppermint), Illici Veri Fructus (star anise), Ginkgonis Semen (ginkgo nut), Cinnamomi Cortex (cinnamon), Cassiae Semen (Sicklepod), Artemisiae Argyi Folium (Korean mugwort), Citri Unshius Pericarpium (tangerine peel), Discoreae Rhizoma (Chinese yam), Schisandrae Fructus (Schisandra berry), Crataegi Fructus (hawthorn berry), powder of green tea
Pure food ingredients	Coffee, Chamomile, Soybean, Parsley, Lavender, Rosemary, Lemongrass, Lemon balm, Bitter gourd

the words “toxicity,” “hormone,” “deformity,” “miscarriage,” and “epileptic seizure” were used, irrespective of evidence level presented in the questionnaire.

Discussion

In East Asia, where traditional medicine using medicinal herbs is practiced, Korea has a very high percentage of medicinal herbs for food use compared to China, Japan, and Taiwan, and there

has always been a risk of mistaking medicinal herbs, which are highly medicinal in nature¹⁾. In addition, various countermeasures have been raised in response to concerns about possible public health hazards caused by indiscriminate use as an ingredient in health functional foods^{1,6)}.

In Korea, safety studies for fetus during pregnancy have been conducted on prescribed herbal medicine by TKM practitioners, however safety studies have not been conducted on medicinal herbs for food use and pure food

Table 3. Summary of the Final Consensus Results

The ingestion caution levels	Ingredient name	Other name	Agreed round	Frequency (times)
1. Do not consume	Ginkgonis Semen*	Ginkgo nut	2nd round	6
	Illici Veri Fructus*	Star anise	1st round	4
	Lavender		1st round	4
	Bitter gourd		1st round	4
	Parsley		1st round	4
2. May be used with caution in dosage and duration after consultation with a TKM practitioner (required)	Rosemary		3rd round	7
	Citri Unshius Pericarpium*	Tangerin peel	2nd round	6
	Discoreae Rhizoma*	Chinese yam	2nd round	6
	Lemongrass		2nd round	6
	Schisandrae Fructus*	Schisandra berry	2nd round	6
	Cassiae Semen*	Sicklepod	3rd round	6
	Foeniculi Fructus*	Fennel seed	1st round	5
	Mori Fructus*	Mulberry	2nd round	5
3. Self-consumption is possible, however consultation with a TKM practitioner is recommended	Cinnamomi Cortex*	Cinnamon	2nd round	5
	Astragali Radix*		1st round	4
	Menthae Herba*	Peppermint	2nd round	7
	Allii Bulbus*	Garlic	1st round	5
	Ginseng Radix*		1st round	5
	Crataegi Fructus*	Hawthorn berry	2nd round	5
	Coffee/green tea*		1st round	4
	Zingiberis Rhizoma*	Ginger	1st round	4
4. Can be consumed without special caution	Artemisiae Argyi Folium*	Korean mugwort	1st round	4
	Lemon balm		1st round	4
	Soybean		3rd round	7
	Chamomile		2nd round	5

Abbreviations: TKM, traditional Korean medicine. * medicinal herbs that are also used for food

ingredients^{14,15}). Therefore, we conducted expert Delphi consensus to assess the potential risks to the fetus during pregnancy of these medicinal herbs for food and pure food ingredients and to develop a minimum level of information that can be provided to the general public. We collected and summarized the literature on fetal safety for 25 ingredients in medicated diet recipes, developed a Delphi consensus questionnaire with the ingestion caution levels, and asked expert panelists to respond.

Ginkgonis Semen (Ginkgo nut), *Illici Veri Fructus* (Star anise), lavender, bitter gourd, and parsley were agreed at the level 1 of “Do not consume”. The dangers of O-methylpyridoxine of Ginkgo nut, a neurotoxin, have been well documented, with reports of adverse effects from overdose, even when baked, and a case of a 2-year-old child experiencing a tonic-clonic seizure after ingestion^{16,17}). Expert opinion gathered during the Delphi also recognized the well-known risk of Ginkgo nut toxicity. *Illici Veri Fructus* has been used in a variety of foods and teas, and traditionally, anise oil has been used as an antispasmodic and labor inducer, with case series of tonic-clonic epileptic seizures reported in infants^{18,19}). Delphi panelists were not inclined to recommend the use of star anise, which is not an essential component of recipe or herbal medicine. Despite the low quality of evidence from known studies including case series reporting controversial result because of the lack of enough information, lavender appeared to have a high perceived risk owing to its hormonal activity and traditional usage as an emmenagogue and abortifacient^{18,20}). Animal studies with pregnant rats or mice have

shown the teratogenic risk of bitter gourd seed, however the decision was made based on the possibility that the seeds could be consumed in combination with the pulp²¹). Parsley, another herb frequently used as a traditional abortifacient, was also deemed high risk owing to reports of seven miscarriages by oral ingestion and injection into the body, the hormonal actions of the extract, and the mutagenic potential of the myristicin component^{22,23,24}).

The following 10 ingredients were recognized as being closer to medicinal herb than food ingredient and were agreed at the level 2 of “consultation with TKM practitioner is required”: Rosemary, *Citri Unshius Pericarpium*, *Discoreae Rhizoma*, lemongrass, *Schisandrae Fructus*, *Cassiae Semen*, *Foeniculi Fructus*, *Mori Fructus*, *Cinnamomi Cortex*, and *Astragali Radix*. The questionnaire included the results of a retrospective clinical study of resveratrol, the main component in *Mori Fructus* and the risks reported in animal studies of the extracts and main components of the other five herb and food ingredients. *Schisandrae Fructus* and *Cinnamomi Cortex* had only reported risks from literature review studies. *Astragali Radix* has been reported to be safe in randomized clinical trials with intravenous injection of extract, however these results should not be interpreted as equivalent to the risks of oral ingestion^{25,26}). When *Astragali Radix*, *Citri Unshius Pericarpium* and *Discoreae Rhizoma* were administered at 20g/day, 9g/day, and 15g/day, respectively, during the organogenesis period of pregnant mice, *Astragali Radix* showed a significant increase in postnatal death, *Citri Unshius Pericarpium* in fetal resorption, postnatal

death, and late death, and *Discoreae Rhizoma* in polydactyly, postnatal death, and early death compared to the control²⁷). In an observational study of 630 mothers within 3 days postpartum, gestational age was significantly but marginally shorter in the group which used *Foeniculi Fructus* during pregnancy compared to non-use group²⁸). A retrospective data analysis of 3,060 pregnant women who conceived via in vitro fertilization found that women who consistently consumed resveratrol, the main ingredient in *Mori Fructus*, had a higher risk of miscarriage (OR 2.602; 95%CI 1.070-6.325)²⁹). *Cinnamomi Cortex* extract showed a concentration-dependent reduction in contraction on isolated rat uterine strips, demonstrating action on the myometrium³⁰). Citral and myrcene, the main components of lemongrass, have been reported to cause birth defects in rats^{31,32}). A clinical trial covered in the literature review reported that a 3-day administration of *Schisandrae Fructus* 70% ethanol-derived tinc caused induction of labor and increased labor induction in multipara¹⁸). Rosemary water extract has been reported to cause an increased number of anomalous embryos and prolonged embryo retention in pregnant rats³³). Reduced fetal weight was reported when emodin, a major component of *Cassiae Semen*, was administered to pregnant mice³⁴).

Factors that may have influenced the expert panelist's decision-making process in reaching an overall consensus included the degree of overdose potential in the domestic environment, the frequency of use as an ingredient in herbal medicines or as a food, and the risk in the first trimester of pregnancy. We also estimated that

ingredients with more perceived risk terms in the literature summaries, such as "toxicity," "hormones," "malformations," "miscarriage," and "epileptic seizures," were more likely to had a higher risk rating by panelist.

In some cases, each panel's previous questionnaire response changed in the next round. We interpreted this phenomenon as a shift in thinking because the results of the Delphi responses and opinions were shared with the panelists, therefore they could see and compare their own responses and opinions within the overall responses again. This sharing process has the effect of forcing panelists to rethink their decisions from a different angle, leading to clearer judgements³⁵).

We suspected that the expert panelists were most concerned with the gap between expert and public views in their assessment and rating, as the public use of medicinal herbs for food is a sensitive topic. An example is the opposition that might be expected if the public were advised to consume a commonly used ingredient after a mandatory consultation with a TKM practitioner. Another example is the concern from the TKM practitioner community when a recommendation is made that certain medicinal herbs can be self-administered by the public. On the other hand, the expert group's assessment of "consultation with TKM practitioner is required" for ingredients such as *Astragali Radix*, *Cinnamomi Cortex*, *Citri Unshius Pericarpium*, *Discoreae Rhizoma*, Rosemary, lemongrass, *Schisandrae Fructus*, and *Cassiae Semen*, which have been frequently used in food in Korea, is expected to be new information for the public.

The significance of this study is that it derived new results through expert consensus on medicinal herbs for food and pure food ingredients, which has not been conducted in Korea to date. Moreover, the consensus on relatively conservative safety assessments for various ingredients used for food is a significant step toward expanding the scope of TKM experts' involvement in public health and ensuring fetal safety in the daily life. In addition, we believe that this study addressed "whether and to what extent TKM practitioners are involved in intake of medicinal herbs for food," and that it also has developmental implications that could lead to specific discussions in the future.

This study has several limitations, including the following. First, because of the ambiguity inherent in the medicinal herbs for food, each panel's internal judgement of risk seemed inconsistent across the entire Delphi process. Factors that contributed to ambiguity included the ease of consumption by the general public, the history of unchecked consumption as an everyday food ingredient, and the anticipated public reactions to agreed caution levels. Second, the significant paucity of published clinical studies on adverse effects of medicinal herbs for food and pure food ingredients may have affected the quality of the Delphi questionnaire and consensus results. Third, this study did not perform an intensive risk discussion focused on the first trimester, which poses the highest fetal risk. Fourth, because we used a relatively small number of expert panelists compared to a typical Delphi study, the result of this study may not have included a sufficiently diverse range of

perspectives.

This study conducted an expert Delphi consensus on ingredients that are readily consumed by pregnant women and have a relatively high number of reported risks for the fetus during pregnancy. Further studies should be conducted according to the trimester of pregnancy, and intensive research should be conducted on medicinal herbs for food, which are recognized as specialized herbal medicines rather than pure food ingredients by TKM practitioners. Based on the results of the Delphi consensus, we expect to be able to provide the general public with relatively evidence-based fetal safety information on medicinal herbs for foods that are on the borderline between herbal medicine and food in Korea, as well as food ingredients that are easy for pregnant women to consume.

Conclusion

Based on the consensus of a seven-member expert panel of TKM gynecologists, *Ginkgonis Semen* (Ginkgo nut), *Illici Veri Fructus* (Star anise), lavender, bitter melon, and parsley should be avoided by pregnant women. For rosemary, *Citri Unshius Pericarpium*, *Discoreae Rhizoma*, lemongrass, *Schisandrae Fructus*, *Cassiae Semen*, *Foeniculi Fructus*, *Mori Fructus*, *Cinnamomi Cortex*, and *Astragal Radix*, the level 2 advisory may be recommended to use with caution and to consult a TKM practitioner for advice on consumption, dose, and duration. *Menthae Herba* (peppermint), *Allii Bulbus*, *Ginseng Radix*, *Crataegi Fructus*, Coffee or green tea, *Zingiberis Rhizoma*, *Artemisiae Argyi Folium*, Lemon balm

are agreed to be relatively safe to consume and may be recommended with the level 3 advisory, with a recommendation to consult a TKM practitioner if necessary.

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