Executive Summary

Assessment of clinical safety and efficacy for weight loss supplements (garcinia cambogia extract, irvingia gabonesis seed extract) in humans

Chaemin Shin[1], Jooyeon Park[1], Ji Jeong Park[1],

Sung Woo Seo[1], Jung Im Shim[1]

[1] National Evidence-based Healthcare Collaborating Agency

▢ Background

Ⅰ. Garcinia cambogia extract and Irvingia gabonesis seed extract

Garcinia cambogia, a member of the Guttiferae family, is a tropical plant native to Southwestern India. Its extract is made using the peel of the fruit, which contains 10–30% of an active substance called hydroxycitric acid (HCA). HCA, an adenosine triphosphate (ATP) citrate lyase inhibitor, has been reported to induce weight loss by inhibiting fat production within the body and to suppress appetite by increasing serotonin secretion in the brain (Semwal RB et al., 2015). Products containing Garcinia cambogia extract that are marketed in Korea and abroad contain 20–60% HCA.

Wild mangos (scientific name: Irvingia gabonesis) are the fruit of a tree that is native to central and western Africa. Mango, African mango, wild mango, dika nut, and bush mango are common names of this fruit. Irvingia gabonesis seed extracts contain high concentrations of saturated fat and have been used in cosmetics and food as a thickener. On the basis of a report that this extract can induce weight loss in Caucasians by reducing blood leptin levels and inhibiting fat production (Oben J et al., 2008), food supplements that claim to induce weight loss are currently sold in domestic and foreign markets.

Ⅱ. Reports of supplement-related adverse effects and adverse reactions in Korea

As you can see on the screen, the food supplement industry is continually growing worldwide. As of 2012, the global food supplement market is worth approximately 96.1 billion US dollars, which is approximately 9.7 trillion Korean won. As of 2013, the Korean food supplement market is worth approximately 1.79 trillion won.

Anyone can easily access information regarding Korean weight loss products online. According to the Ministry of Food and Drug Safety (MFDS), 335 Garcinia cambogia extract products from 74 companies are currently on the market. As of 2015, domestic sales of Garcinia cambogia products had reached 25.9 billion won, and that of Irvingia gabonensis seed products had reached 17.3 billion won.

The recent upsurge of food supplement sales online has sparked heated debate regarding the efficacy and safety of these products. A total of 6,775 cases of weight loss- or diet-related consumer injuries were reported to the Consumer Injury Surveillance System (CISS) and Consumer Counseling Network (1372) from 2012 to October 2015, of which 5,184 cases involved those concerning diet products or supplements. Of the 421 reports of supplement adverse reactions submitted to the MFDS from January to July 2015, the highest number of cases involved Cynanchum bungei (131 cases). The second highest number involved diet products, with 38 cases involving Garcinia cambogia extract (9%) and 13 cases involving Irvingia gabonensis seed extract (3%).

Adverse reactions reported to the Korean Consumer Agency (KCA) include skin conditions, allergy, facial edema, headache, fever, inertia, mood swings, and depression. Foreign reports have documented adverse reactions such as jaundice, dyspnea, convulsion, headache, elevated blood pressure, anxiety, perspiration, nausea, vomiting, rash, edema, tachycardia, blepharospasm, inertia, and renal impairment. Particularly, in response to 23 cases of suspected nephrotoxicity, the United States Food and Drug Administration (FDA) ordered a recall of a specific HCA-containing product (i.e., Hydroxycut) in 2009.

However, a considerable number of food supplements that are currently marketed worldwide have not been adequately tested for human use through clinical trials. Therefore, it is important to analyze the clinical evidence of products that are frequently sold but have high risks of adverse effects in order to understand their safety.

By educating consumers to make informed decisions, we can protect the health of the public.

▢ Objectives

In this context, we aimed to develop a framework for policy-making guidelines of weight loss supplements, by developing an informational booklet on the use of some more popular supplements. To this end, we analyzed the clinical safety and efficacy, as well as reports of adverse effects and adverse reactions to these products, and we received consultation from clinical specialists. The specific objectives of this study are as follows.

First, to analyze the clinical safety and efficacy of Garcinia cambogia extract and Irvingia gabonensis seed extract.

Second, to analyze the adverse effects or reports of adverse reactions involving Garcinia cambogia extract and Irvingia gabonensis seed extract.

Third, to develop an informational booklet about Garcinia cambogia extract and Irvingia gabonensis seed extract.

▢ Methods

Ⅰ. Systematic review

We examined the latest evidence of the clinical safety and efficacy of weight loss supplements via a systematic review. The subject pool was not limited, and subjects included those who took Garcinia cambogia extract-containing products or Irvingia gabonensis seed extract-containing products. As major outcome variables, weight loss (body weight loss, changes in BMI, reduced body fat), metabolic indices (reduced waist circumference),

and hematological changes (leptin, cholesterol) were considered indices of efficacy; mortality, metabolic disorders, cranial nerve/mental manifestations, and other adverse effects, including those of the skin, gastrointestinal, liver/renal/urinary, and cardiovascular/respiratory systems, were considered indices of safety.

The literature search was performed in the Korean databases KoreaMed, KISS, KMBASE, RISS, and KiSTi, and the foreign databases Ovid-Medline, Ovid-EMBASE, and CENTRAL (Cochrane Library). Risk of bias was assessed for the selected literature after applying primary and secondary selection/exclusion criteria, using the Cochrane's Risk of Bias (RoB) and Risk of Bias for Nonrandomized studies (RoBANS).

Ⅱ. Analysis of adverse reactions reported by consumers

To review the adverse reactions that occurred after taking the supplements, we collected detailed data using the submitted reports of adverse effects and adverse reactions for the past two years with cooperation from the KCA and MFDS.

From these data, we exported a subset of information to Microsoft Excel, specifically:

- Personal information (age, sex)
- Product information (name of product, channel of purse)
- Symptoms (major symptoms, duration/amount of intake, onset, existing morbidity, treatment, persistence of symptoms, and other details)

We received the raw data from corresponding departments after all personal identification information was deleted (i.e., no personal identifying information was retained, other than sex and age). We then analyzed the adverse effects and adverse reactions based on the symptom information provided. In addition, the analytical methods were established, and the risks and toxicities were analyzed based on consultation from relevant clinical societies, including the Korean Association of the Study of the Liver.

Ⅲ. Dissemination of study results

The ultimate goal of this study was to provide scientific evidence of the safety of weight loss supplements (Garcinia cambogia extract and Irvingia gabonensis seed extract) and to disseminate the appropriate use of these products to the public. Thus, we developed a promotional video and an informational leaflet based on the results of the systematic review and policy conference.

As our target audience was the general public, we aimed to increase readability by making a 4-page leaflet (including the title page) and limiting the content to essential information. The first draft of the leaflet was written by the research team and modified based on advice from clinical gastroenterology specialists. Furthermore, to expand the target audience to include foreign residents in Korea to promote recognition of our team abroad, we also decided to make an English version of the leaflet.

Because multiple domestic and foreign research institutions actively utilize YouTube or Facebook as their channels to disseminate study results, we also decided to publish a promotional video on social media. The first version of the promotional video was written by our research team based on the content of the leaflet. Our research team met with a professional promo video producer to discuss details, including length of the video, objectives, content, and production schedule. Owing to the limitations of time and cost, we decided to include the findings of the “Research for safe use of probiotics” in this video also.

The scenario and characters of the promotional video were reviewed via emails, and the first draft of the video was discussed in a face-to-face meeting.

▢ Results

Ⅰ. Assessment of clinical safety and efficacy of weight loss supplements

1) Garcinia cambogia extract

The initial search produced 3,457 citations in foreign databases and 468

citations in Korean databases. Following exclusion of simple overlaps, 1,332 articles were selected for further consideration. After examination of abstracts and titles, the texts of 127 articles were reviewed, and 73 articles were finally selected based on the inclusion and exclusion criteria. In terms of study design, 35 articles involved either clinical trials or pre- and post-treatment comparisons, and 38 were case reports, of which 12 involved HCA-containing products and 26 involved a specific product (i.e., hydroxycut).

A quality assessment of the randomized controlled trials (RCTs) among the selected studies showed that many of them had potential risks of allocation concealment or blinding biases, but none of them had detection or reporting biases. However, most of the studies were privately funded, calling for careful interpretation of the results. Many of the non-RCTs had confounding variables and risk of bias for incomplete outcome data, but they had no particular risks of biases for other indices. With regard to case reports, many of them provided relevant measurements, but we could not determine their validity owing to the one-time nature of the measurements. Most case studies only drew potential associations and not a clear causal relationship. Furthermore, it was difficult to determine whether potential problems existed with the supplements, as few studies provided probable biological mechanisms or sufficient information.

We assessed clinical efficacy based on 34 articles and found that, compared to control groups, Garcinia cambogia extract significantly reduced body weight (body weight, waist or hip circumference). However, follow-up periods were short (less than 12 weeks), and there was heterogeneity in the study results. Furthermore, many studies were funded by parties with vested interest.

○ Weight loss indices: changes in body weight, body fat, BMI

- Body weight: The HCA group had a significant weight loss compared to the control group in 13 studies, but there were no significant differences in weight loss reported between the two groups in 10 studies.
- Body fat: The HCA group had a significant reduction of body fat compared to the control group in 12 studies, but there were no significant differences in body fat reported between the two groups in

seven studies.

- BMI: The HCA group had a significant decrease of BMI compared to the control group in nine studies, but there were no significant differences in BMI reported between the two groups in eight studies.

○ Metabolic indices: changes in waist and hip measurements

- The HCA group had a significant reduction of waist or hip circumference compared to the control group in four studies, but there were no significant differences in circumference reported between the two groups in nine studies.

○ Hematological indices: changes in leptin and cholesterol

- Leptin: Leptin levels decreased after product intake in three studies, but there were no significant differences in leptin levels reported between the two groups in two studies.
- Cholesterol: The intervention group had significant improvements in total cholesterol (TC) levels than did the control group in 4 studies, but there were no significant differences in TC levels reported in 10 studies.

There were no reports of severe adverse effects, and three studies reported no adverse effects. In 15 articles, the following types of adverse effects were identified based on clinical trials and pre- and post-treatment comparisons.

- Gastrointestinal system: heartburn, nausea, abdominal pain, abdominal bloating, abdominal discomfort, intestinal gas, gastritis, gastric disorder, dyschezia, diarrhea/constipation
- Metabolic disorder: perspiration, thirst
- Skin: skin rash
- Liver/kidney/urinary system: frequent urination, diuresis, cystitis, edema
- Cranial nerves/mental: vertigo, insomnia, nervousness, headache, lower limb spasms
- Cardiovascular/respiratory system: numbness/cold hands and feet, respiratory

disturbance, upper respiratory tract infection, bronchitis

- Others: lower back pain, articular pain, fatigue, cold, pharyngolaryngitis, toothache, menstrual irregularity/pain, weakness

We analyzed 12 case studies and found reports of liver damage, such as acute hepatitis and liver failure, and heart disease, such as acute myocarditis and tachycardia, in people who took Garcinia cambogia extract products (n = 16). Other cases involved rhabdomyolysis, serotonin toxicity, hypoglycemia, hypertension, and stress. According to a Korean case report by Lee et al. (2014), a 39-year-old woman (BMI 29.12 kg/m2), who did not have underlying disease and was not taking other medications, was admitted to hospital for symptoms of abdominal discomfort, loss of appetite, nausea, indigestion, fatigue, and jaundice after taking an HCA-containing supplement for weight loss purposes. Liver biopsy results showed lobular necrosis, fibrosis, and bile congestion, suggesting liver damage. The patient showed improvement after four weeks of inpatient treatment and four months of follow-up.

2) Irvingia gabonesis seed extract

The initial search produced 3,541 citations in foreign databases and 589 citations in Korean databases. Following the exclusion of simple overlaps, 458 articles were selected for further consideration. After examination of abstracts and titles, the texts of 11 articles were reviewed, and 7 articles were finally selected based on the inclusion and exclusion criteria. In terms of study design, three studies were RCTs, two were pre- and post-treatment comparisons, and two were case reports.

A quality assessment of the RCTs showed that many had uncertain risks of bias for random sequence generation or allocation concealment, but none had a risk of bias for blinding. However, most of the studies were privately funded or used selective reporting, calling for careful interpretation of the results. Many of the non-RCTs had confounding variables and a risk of bias for incomplete outcome data, and one study had a high risk of bias for selective reporting of outcomes. Similar to the studies with Garcinia

cambogia extract, these case studies provided relevant measurements, but we could not determine their validity. With regard to causal relationships, one study implied a direct association, while the other study could not confirm the presence of such an association. Furthermore, it was difficult to determine whether potential problems existed with the products, as few studies provided probable biological mechanisms or sufficient information.

The findings of the three RCTs showed that, compared to the control groups, the Irvingia gabonensis seed extract group had reduced waist measurements and TC levels. There were declining trends in body weight and body fat, but the differences were not statistically significant.

The following adverse effects were reported in the treatment groups that were given Irvingia gabonensis seed extract products: hepatomegaly, chronic renal failure, jaundice, abdominal discomfort, inertia/malaise, headache, sleep disturbance, edema, and skin troubles. Both the treatment and control groups had adverse effects in two RCTs, and both of these studies reported that the incidence of adverse effects was similar for both groups. Chronic renal failure and hepatotoxicity were reported in the two case reports, but the latter improved after cessation of supplement use.

Ⅱ. Analysis of adverse reactions reported by consumers in Korea

As of 2015, 3,220 cases of adverse reactions of food supplements were reported to the MFDS, of which 243 cases involved Garcinia cambogia extract and 17 cases involved Irvingia gabonensis seed extract.

Most of the adverse reactions involving Garcinia cambogia extract and Irvingia gabonensis seed extract were gastrointestinal or skin-related, and only 21 cases involved the liver/renal/urinary system. Consumers, suppliers, and an expert reported 198, 22, and 1 case(s), respectively. With the exception of two cases, suspected liver/renal/urinary adverse reactions for Garcinia cambogia extract supplements were classified as “edema.” In one of the two exceptions, the patient developed conjunctivitis after taking the supplement for about six weeks. This patient was told at a clinic to visit a larger hospital for suspected liver overload, but supplement involvement was unclear. In the other exception, the patient underwent a medical check-up

after about three months of taking Garcinia cambogia extract supplement, and the results indicated a low glomerular filtration rate and gastrointestinal disturbance. The patient's symptoms (e.g., vomiting) persisted even after two weeks of supplement cessation.

Adverse reactions pertaining to Garcinia cambogia extract intake reported to the KCA between 2012 and October 2015 include skin problems, fever, vertigo, vomiting, anal and pudendal allergies, facial edema, headache, mood swings, depression, and lethargy.

Ⅲ. Leaflet and promotional video production

The informational booklet, "Appropriate use of weight loss products for consumers," comprises five categories of information, including definitions of Garcinia cambogia extract and Irvingia gabonensis seed extract, precautions for use and purchase, and countermeasures for adverse reactions. The informational booklet was designed as a 4-page leaflet of half the size of A4 paper to promote portability. We plan to disseminate the leaflet domestically and abroad via our website and paper print.

The 100-s promotional video was produced as an animation with the contents listed below. We tried to keep the content simple and concise, using a familiar character to help the public understand it easily. We plan to disseminate the video in collaboration with our knowledge and information dissemination team via our website, YouTube, Blog, Facebook, and mailing service.

- Introduce Garcinia cambogia extract and Irvingia gabonensis seed extract products
- Efficacy of Garcinia cambogia extract and Irvingia gabonensis seed extract supplements
- Adverse effects of Garcinia cambogia extract and Irvingia gabonensis seed extract supplements
- Countermeasures for adverse reactions from food supplement intake

▢ Conclusions

In this study, we analyzed the safety and efficacy of Garcinia cambogia extract and Irvingia gabonensis seed extract supplements—weight loss products that are frequently sold and have suspected adverse effects—via a systematic review and analysis of adverse reactions. Our conclusions are as follows.

A systematic review revealed that Garcinia cambogia extract supplements had short-term weight loss effects (within 12 weeks). However, further studies are required to substantiate these findings, as the existing studies were of limited quality and efficacy. Furthermore, multiple adverse reactions have been reported, including liver damage, heart disease, rhabdomyolysis, gastrointestinal disturbance, edema, red eye, depression, and insomnia. Analysis of the adverse reactions reported to the MFDS and KCA could not confirm a causal relationship owing to limited data, but these products should be taken with caution, as there have been reports of systemic skin trouble, abdominal pain, vertigo, vomiting, and edema.

Regarding Irvingia gabonensis seed extracts, a systematic review showed that these products were effective at reducing waist circumference and TC levels. However, additional studies are required to substantiate these findings because the existing studies were of low quality and one study used inappropriate groups for comparisons. In terms of safety, adverse effects such as chronic renal failure, hepatotoxicity, headache, sleep disturbance, and intestinal gas have been documented in the literature. Analysis of the adverse reactions reported to the MFDS and KCA could not confirm a causal relationship owing to limited data, but these products should be taken with caution, as there have been reports of skin trouble, vomiting, and edema.

On the basis of these conclusions and considering the opinions of pertinent societies, associations, and policy experts obtained via meetings and policy forums, we propose the following policies.

1. Ameliorate the licensing system, including clarifying grade-specific

evaluation criteria for food supplements.

2. Harmonize the process of submitting reports of adverse effects involving food supplements (i.e., reporting, standardized classification, follow-up, and analysis).
   - Develop a standardized classification system for reporting adverse reactions.
3. Develop an adverse effects reporting system for health care professionals and consistently monitor it by organizing an expert committee.
4. Promote appropriate (safe) use of products by providing accurate information to the public, such as implementing labeling (precautions) requirements and developing informational booklets.
   - A product use guideline is needed to prevent adverse effects.
5. Provide an institutional strategy and guideline for quality assessment and follow-up management of food supplements.

▢ Plain Language

Korean

▢ Acknowledgement

This Research was supported by National Evidence-based Healthcare Collaborating Agency (NECA) funded by the Ministry of Health and welfare (grant number NECA-H-16-001).

Key words

Weight loss supplements, Irvingia gabonesis, Garcinia cambogia, Safety, Efficacy, Adverse effects, Adverse reactions