

Does the Health Supplement HemoHIM Cause Liver Injury?

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건강기능식품 헤모힘이 간손상을 일으키는가?

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Abstract This study aimed to examine the safety of HemoHIM, a dietary supplement containing methoxsalen. HemoHIM is a dietary supplement marketed globally, and a competitor to ginseng. It has been reported to contain methoxsalen, a plant extract for treating psoriasis and vitiligo. Methoxsalen is known to cause hepatotoxicity, but most of the cases has been reported from ingestion as a drug, not a food. There are no reports of hepatotoxicity from the consumption derived from natural products such as *Angelica gigas*, *Cnidium officinale*, and *Paeonia lactiflora*, which are the main ingredients in the HemoHIM. However, a recent case of acute hepatitis was reported in Hong-Kong after ingestion of HemoHIM. It is difficult to conclude that hepatitis was caused by HemoHIM, because there was no check of co-occurring medications with a higher risk of hepatotoxicity, no description of the progress, no quantitative comparison of methoxsalen in HemoHIM to it in common foods such as carrots and celery, and no description of the patient's underlying diseases. On the other hand, there was a study that suggest hemoHIM is safe, and that study had adequate number of subjects even though more studies are needed to ensure safety.

Key Words : Hepatotoxicity, Herbs, Hemohim, Causality assessment, Function food

요약 이 연구는 메톡살렌이 함유된 건강 보조 식품인 헤모힘의 안전성을 조사하는 것을 목표로 했다. 헤모힘은 전 세계적으로 판매되는 건강 보조 식품으로 인삼과 경쟁 관계에 있는 제품이다. 진선 및 백반증 치료용 식물 추출물인 메톡살렌이 함유되어 있는 것으로 보고되었다. 메톡살렌은 간독성을 유발하는 것으로 알려져 있지만, 대부분의 사례는 식품이 아닌 의약품으로 섭취했을 때 발생한 것으로 보고되었다. 헤모힘의 주원료인 당귀, 천궁, 백년초 등 천연물에서 추출한 성분의 섭취로 인한 간독성 보고는 아직 없다. 그러나 최근 홍콩에서 헤모힘 섭취 후 급성 간염이 발생한 사례가 보고되었다. 간독성 위험이 높은 약물을 함께 복용했는지 확인되지 않았고, 경과에 대한 설명이 없으며, 당근, 셀러리 등 일반 식품에 함유된 메톡살렌과 헤모힘의 메톡살렌을 정량적으로 비교하지 않았으며, 환자의 기저 질환에 대한 설명이 없어 헤모힘으로 인한 간염이라고 단정하기는 어렵다. 반면에 피험자 수가 충분하였던 헤모힘이 안전하다는 연구도 있다. 안정성을 주장하려면 더 많은 연구 논문이 필요하다고 생각된다.

키워드 : 간독성, 생약, 헤모힘, 인과관계평가, 기능성식품

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1. Introduction

Methoxsalen is an organic compound found in various natural products including celery, parsley, angelica, and bakuchi seed. It has recently been used as an ingredient in health supplements[1]. It is also used in psoralen and long wavelength (UVA) irradiation therapy for skin disorders, including psoriasis and vitiligo[2]. Methoxsalen is currently classified as “less-drug-induced liver injury (DILI)-concern” by the United States Food and Drug Administration (FDA) and severity class 3 by the National Institutes of Health (NIH) LiverTox database[3], Table 1.

Table 1. Drug classification according to severity class and concern for drug-induced liver injury

LTKBID*	Compound Name	Severity Class [†]	vDILIConcern [‡]
LT00084	Diclofenac	8	Most-DILI-Concern
LT00080	Dantrolene	8	Most-DILI-Concern
LT00060	Carbamazepine	7	Most-DILI-Concern
LT00004	Acetaminophen	5	Most-DILI-Concern
LT00258	Atorvastatin	5	Most-DILI-Concern
LT00175	Amlodipine	5	Less-DILI-Concern
LT01537	Methoxsalen	3	Less-DILI-Concern
LT00267	Quetiapine	3	Less-DILI-Concern
LT00625	Sertraline	3	Less-DILI-Concern
LT02009	Vitamin C	0	No-DILI-Concern

*: LTKBID (Liver Toxicity Knowledge Base Identification)

[†]: Severity class ranges from 0-8, with corresponding drug-induced liver injury (DILI) concern: No-DILI (1-2), Less-DILI (3-6), and Most-DILI (7-8) Concern

[‡]: DILI Concern is categorized into 3 groups: No-DILI, Less-DILI, and Most-DILI-Concern

Cases of hepatotoxicity after methoxsalen consumption are rare. The reported cases involved consumption of a 40-mg PO methoxsalen dose with exposure to UV light for a total of 40 courses, long-term consumption of a high dose of bakuchi seed, consumption of more than 10 times the usual dose by a menopausal woman, and consumption of 4 bakuchi tablets OD x7/12 followed by 2 tablets PO x2/12[4-6].

In Hong Kong and Taiwan, there are no standard specifications and regulations regarding methoxsalen

in health supplements or food, and Taiwan has only announced the testing method for measuring methoxsalen. To date, European Food Safety Authority (EFSA) report in 2016 on the safety of Novel Food called EstroG-100TM, an extract derived from a hot-water mixture of three herbal roots including *Angelica gigas* is the sole safety assessment for health supplements containing methoxsalen [7].

A recent study published in Hong Kong revealed cases of hepatotoxicity after consumption of the health supplement HemoHIM (Atomy; Gongju, South Korea)[8]. HemoHIM is mixture extract of *Angelica gigas*, *Cynanchum wilfordii*, and *Paeonia japonica*, and contains a trace amount of methoxsalen from *Angelica gigas*. The product is known for immunomodulatory effects which has been confirmed through studies showing proportional increase in NK cell activity and Interferon- γ and Interleukin-12 levels over the duration of HemoHIM intake compared to the control group. HemoHIM is now a widely known supplement and has made two billion dollars in sales since it was launched. Its popularity has steadily increased, and it is now a competitor of ginseng in South Korea. Therefore, reviewing the safety issues associated with HemoHIM is important for public health.

2. Discussion

Methoxsalen should be taken according to its recommended dose. Stephens RB. and Cooper A. (1999) described a case of a 55-year-old woman with psoriasis vulgaris who developed hepatitis after being treated with oral 5-methoxypsoralen and UVA photochemotherapy [4]. The patient had a history of cholestatic hepatitis after flucloxacillin intake six years ago. The authors suggested that a thorough history of adverse drug reactions must be taken before initiating treatment. Nam et al.(2005) described a case of toxic hepatitis after more than

10 times the normal dose of *Psoralea corylifolia* was taken to treat osteoporosis as an alternative medicine regimen[5]. The authors warned of potential hepatotoxicity following methoxsalen consumption, especially in cases of overdose. Teschke R. and Bahre R.(2009) reported a case involving a female who developed severe liver failure (alanine aminotransferase [ALT], 601 U/L; aspartate aminotransferase [AST], 663 U/L; Bilirubin, 5.0 mg/dL) after 9 months of self-treatment with various Indian Ayurvedic herbal products for her vitiligo[6]. After discontinuation of those products, rapid improvement was observed. The authors considered the bakuchi tablets containing extracts from *Psoralea corylifolia* as the major etiologic factors for hepatotoxicity. However, other drugs that the patient was concurrently taking, such as Khadin tablets containing extracts from *Acacia catechu* leaves, Brahmi tablets containing *Eclipta alba* and *Bacopa monnieri*, and Usheer tea prepared from *Vetivexia zizanioides* are also linked to hepatotoxicity.

Analyses of the cases above revealed that one case of hepatotoxicity originated from the direct form of methoxsalen, while the other two cases arose from *Psoralea corylifolia* use. A previous study showed that the molecular weight of methoxsalen in *Psoralea corylifolia* is approximately 216.20 g/mol[9]. In contrast, there have been no reported cases of hepatotoxicity from methoxsalen extracted from *Angelica gigas*, *Cnidium officinale*, or *Paeonia lactiflora*, the main components of HemoHIM[10].

CK chan et al. reported four cases of isolated liver injury from HemoHIM consumption and warned about the possible toxicity of methoxsalen[8]. Quantitative causality was assessed using the Roussel Uclaf Causality Assessment Method (RUCAM). HemoHIM supplementation ranged from 2 weeks to 5 months, and all four cases achieved a score of six using the RUCAM. The patients' drug history included regular supplementation with HemoHIM, as well as intake of

atorvastatin, amlodipine, menopause formula (dong quai extract and chasteberry extract), calcium supplement, quetiapine, and sertraline. The patients' peak serologic ALT, alkaline phosphatase, and total bilirubin levels were provided to support the study. All four patients showed major improvement in hepatic function after cessation of HemoHIM supplementation. This is the first review to report on the side-effect profile of HemoHIM. Nonetheless, this review had obvious limitations. Potential confounders, such as comorbidities, weight or body mass index, blood glucose level, and concurrent intake of other medications with known hepatotoxic properties, were not analyzed because of unavailability of information[3,8],[Table 1].

The diagnosis of DILI depends largely on a compatible history, intake of a drug known to cause liver injury, and sequential exclusion of common etiologies of liver injury. Chemical and toxicological analyses to isolate and test product ingredients for toxic potential should also be performed[11,12]. Additionally, reports on hepatotoxicity should include detailed information on dosages of all suspicious substances that may cause liver injury, cessation of these substances, duration of recovery after discontinuation, treatment administered for hepatitis, and changes in liver function during treatment. Data on diagnosis, progression, and other relevant details were not available in existing reports. With the current trend of polypharmacy, it is extremely challenging to definitively identify causative drugs for hepatotoxicity. Since all reported patients were taking multiple drugs or supplements, the role of these drugs in causing hepatotoxicity must be considered. A critical error identified in the reports was the lack of information on the dosage and duration of drugs and other supplements, particularly atorvastatin, which has a higher risk of causing DILI than methoxsalen. The FDA classifies atorvastatin as "Most-DILI-Concern." Amlodipine also has a higher severity class than methoxsalen, while quetiapine and sertraline are

classified as “Less-DILI-Concern,” similar to methoxsalen[3]. The second case report also lacked detailed information on the duration and amount of dong quai, chasteberry, and black cohosh extract consumption. Since these extracts are not drugs, the FDA has not classified their risk for causing DILI. However, computational analysis performed in a previous study showed that these extracts contain botanical constituents with hepatotoxic potential [13]. Only the patient in the fourth case report had concurrent intake of drugs not known to cause hepatotoxicity. However, considering the lack of information, inability to rule out other causes of hepatotoxicity, and the amount of HemoHIM consumed in the first three case reports, other confounding factors, such as underlying diseases, must be considered.

Further analysis of the components of HemoHIM must be done. As methoxsalen is ubiquitously found in vegetables, such as celery and carrots, that are included in daily meals, a comparative analysis between the amount of methoxsalen in natural food and HemoHIM must be performed, and the mechanism by which methoxsalen causes hepatotoxicity should be discussed[1].

Angelica gigas, the perennial aromatic herb belonging to the Apiaceae family, is the main ingredient of HemoHIM. It was ranked as the tenth most-produced herbal ingredient according to the 2019 yearbook of Korean medicine. It is commonly used in samgyetang, pickles, herbs, ssam vegetables, tea, and beverages, including ssanghwatang and sipjeondaebotang. In addition to methoxsalen, coumarin derivatives, decursinol, 7-demethyl-suberosine, umbelliferone, soimperatorin, xanthyletin, and nodakenin are known components of *Angelica gigas*.

In 2016, the EFSA Panel on Dietetic Products, Nutrition, and Allergies reviewed the safety of EstroG-100™, a dried extract obtained from the steam distillation of the roots of three medicinal plants: *Angelica gigas*, *Phlomisumbrosa* Turcz, and

Cynanchum wilfordii Hemsley. EFSA concluded that the dosage of 175mg/70kg bw/day of EstroG-100TM is considered safe for use as a dietary supplements. The permitted dosage is based on toxicological data and other relevant information provided by the applicant. However, when converted to the maximum content of methoxsalen proposed in the application data (3 mg/g), it corresponds to a maximum dosage of 0.0075 mg/kg bw/day of methoxsalen.[7].

Seo et al. demonstrated the effects of HemoHIM in reducing fatigue and improving exercise performance. Ninety-six healthy patients experiencing fatigue were included in the study. Forty-eight patients consumed HemoHIM twice a day, while the control group consumed a placebo for eight weeks [14]. The exclusion criteria were patients who consumed a substantial amount of alcohol, smoked, had a drug addiction, had a history of underline diseases, were maintained on prescription drugs, or were taking herbal supplements that modulate fatigue. During the study period, the patients underwent four isolated serologic tests, including AST and ALT, to detect hepatotoxicity due to HemoHIM supplementation; however, no significant increase in these transaminase was noted during the study period.

The strength of the previous study lies in the involvement of human subjects. If hepatotoxicity was a complication of HemoHIM supplementation, this would have manifested through the elevation of liver enzymes, and there would have been noticeable increase in the fatigue experienced by patients. The sample size was not a limitation of the previous study since this was determined by reviewing other studies that confirmed the effect of supplement intake on exercise performance or fatigue level [15 ,16]. Nonetheless, the study was limited by the fact that, in reality, supplements are consumed daily for substantial periods of time. Further studies with larger sample sizes and longer study durations may support the validity of these findings.

3. Conclusion

The use of methoxsalen in photochemotherapy for psoriasis has long been established [2]. In addition, methoxsalen is a naturally-occurring constituent of food, such as celery and parsley, which are frequently consumed [1]. Most foods and drugs can be associated with adverse reactions. Even green tea, a common dietary component, is a major agent linked to hepatotoxicity [12]. What is more important is knowing whether such adverse effects are preventable. Because of its widespread use, identifying the preventable side effects of HemoHIM is beneficial for public health.

Case reports on hepatotoxicity from methoxsalen are attributed to consuming either the direct form of methoxsalen or natural products, such as *Psoralea corylifolia*, that contain methoxsalen. There have been no case reports on the development of hepatotoxicity after consumption of methoxsalen that was extracted from *Angelica gigas*, *Cnidium officinale*, and *Paeonia lactiflora*, the main components of HemoHIM[10]. Additionally, since trace amounts of methoxsalen extract are present in HemoHIM, the likelihood of developing hepatotoxicity from HemoHIM is extremely low.

Case reports investigating methoxsalen-associated hepatotoxicity should be highly objective and detailed. However, the available reports from Hong Kong on this issue contain several limitations and lack sufficient evidence to suggest that HemoHIM directly causes hepatotoxicity. Further studies with large sample sizes are required to definitively confirm whether methoxsalen is hepatotoxic.

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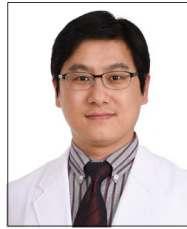
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