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Original Article

Asari Radix et *Rhizoma* consumption lacks relevance for hepatocellular carcinoma in patients: A retrospective cohort study

Zhi-e Fang [a,b,1], Yuming Guo [a,b,1], Zhilei Wang [a,b], Tingting He [a,b], Jiabo Wang [a,b], Zhaofang Bai [a,b], Xiaohe Xiao [a,b,*]

[a] Department of Hepatology, Fifth Medical Center of Chinese PLA General Hospital, Beijing 100039, China
[b] China Military Institute of Chinese Materia, Fifth Medical Center of Chinese PLA General Hospital, Beijing 100039, China

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ABSTRACT

Objective: Although some studies have linked *Asari Radix* et *Rhizoma* (*Asari Radix*) administration to hepatocellular carcinoma (HCC), few studies have examined the association between the development of HCC and use of *Asari Radix* among patients in mainland China. This study aimed to evaluate the real-world association between *Asari Radix* and HCC in patients to strengthen the understanding of *Asari Radix* safety.

Methods: A retrospective cohort study among hepatitis B virus (HBV)-monoinfected patients and non-HBV-monoinfected patients were performed. Patients over 18 years of age were eligible for inclusion. Prescription records of inpatients and outpatients were inquired to distinguish *Asari Radix* users and nonusers. The risk of developing HCC among *Asari Radix* users and nonusers in the HBV cohort and the non-HBV cohort was analyzed.

Results: There were 49 500 HBV and 133 148 non-HBV patients involved in the two cohorts. Among HBV patients (2 901 users; 46 599 nonusers), the prevalence of HCC in *Asari Radix* users was lower than that in nonusers (145.70 *vs.* 265.43 per 10^5). Among non-HBV patients (5 042 users; 128 106 nonusers), the prevalence of HCC in *Asari Radix* users was lower than that in nonusers (81.62 *vs.* 134.11 per 10^5). None of the hazard ratios (HRs) of *Asari Radix* exposure ranging from 1 g to 200 g in the two cohorts showed correlation between *Asari Radix* exposure and hepatocarcinogenesis.

Conclusion: An obvious irrelevancy was found between the consumption of *Asari Radix* and HCC development both in patients with and in those without HBV infection. Use of *Asari Radix* under 200 g appears safe in terms of HCC risk in the Chinese population; further prospective studies are needed to confirm our results.

1. Introduction

Asari Radix et *Rhizoma* (*Asari Radix*) is one of the most commonly prescribed herbs in Chinese medicine therapy (Cao et al, 2015). Its application was first recorded in the *Shennong's Classic of Materia Medica* (Shennong Bencaojing in Chinese) and widely used to treat cold, cough, and toothache, rheumatic arthralgia since antiquity (Wen et al., 2014; Zhao et al., 2008). There is a recordation of minor toxicity about *Asari Radix* in the Chinese Pharmacopoeia and some studies have disclosed that toxicity was related with safrole (Pharmacopoeia Commission of the People's Republic of China, 2020; Chiang et al., 2011; Yang et al., 2018). Recently, some researchers pointed out aristolochic acids (AAs) have induced the onset of HCC (Ng et al., 2017). Nowadays, almost 200 types of Chinese traditional patent medicines containing *Asari Radix* were found in the database of National Medical Products Administration on the Chinese mainland and low levels of AAs has been still detected in the parts of roots, which aroused scholars concern about the safety (Grollman & Marcus, 2016; Liu et al., 2021).

AAs were known of nephrotoxicity and carcinogenicity and listed as Group I carcinogens by the International Agency for Research on Cancer in 2002, thereby withdrawn from a number of countries (Nault & Letouzé, 2019). In the latest study, there was a significant linear dose–response relationship between the consumption of AA and HCC patients with hepatitis B virus (HBV) (Chen et al., 2018). Interestingly, Chen et al. reported that the consumption of *Asari Radix* had an irrelevant relationship with

* Corresponding author.
E-mail address: pharmacy_302@126.com (X.H. Xiao).
[1] These authors contributed equally to this work.

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hepatocarcinogenesis at an intake below 200 g, thereby disproving the hypothesis that *Asari Radix* has a collaborative role with HBV in the HCC pathogenesis (Chen et al., 2019).

Although there have been some studies about the association between *Asari Radix* and HCC, the results are contradictory (Chen et al., 2019; Ji et al., 2018; Liu et al., 2021). There are a limited number of epidemiological studies on the long-term influence of these relationships between *Asari Radix* and HCC in mainland China. Clinical practice guidelines and healthcare system in mainland China are not in accordance with those in other countries. It is crucial to explore the relationship between AAs and HCC so as to inform prevention and control strategies. Here, we adopted a retrospective population-based study to assess the relationship between *Asari Radix* use and the risk of HCC among HBV and non-HBV patients, and the clinical use of AA-related preparations since the establishment of forbidden AA usage policy in mainland China was analyzed.

2. Patients and methods

2.1. Population and study design

This study was conducted with the approval of the Ethics Committee of the Fifth Medical Center of PLA General Hospital.

We evaluated the association between AAs and HCC in a population-based retrospective study from the Yinzhou Health Information System (YHIS) in Ningbo City, Zhejiang Province, People's Republic of China, between January 1, 2009, and December 12, 2018. The YHIS integrates public, community, and hospital health data, which are stored in the administrative healthcare database including electronic medical records, demographic characteristics, diagnosis information, pathologic findings, as well as clinical medication, including conventional drugs and traditional Chinese medicines (Li et al., 2018).

At the beginning, we excluded missing data and patients born after January 1, 1992, when Chinese HBV vaccination program had begun based on predominant evidence that the application of HBV vaccination significantly weakens the development of HCC. We defined two cohorts, including the HBV cohort and the non-HBV cohort. The diagnostic codes of HBV referred to the 10th edition of the International Classification of Diseases (ICD); the ICD-10 codes for HBV were B16, Z22.502, Z22.503, and Z22.504. Only HBV-infected patients were included in the HBV cohort, while the non-HBV cohort completely excluded HBV cases. Previous studies have found that other cancers, such as urothelial carcinoma, pancreatic cancer, rectal carcinoma, and gastric carcinoma, have a high incidence of metastasis to the liver, so we excluded patients with liver metastases (Chen et al., 2019). In addition, some studies have shown that the incidence of HCC decreases through antiviral therapy (Kim et al., 2018; Owusu Sekyere et al., 2019); thus, we excluded patients who had used anti-HBV drugs before January 2009 to minimize their influence.

2.2. Exposure to AA-containing medication

Since 2003, Guangmutong (*Aristolochia manshuirensis* Kom.), Qingmuxiang (*Aristolochia debilis* Sieb. et Zucc.), Guangfangji (*Aristolochia fangchi* Y. C. Wu ex L. D. Chou et S. M. Hwang), and Xungufeng (*Aristolochia mollissima* Hance) have been officially prohibited in China; however, Xixin (*Asarum heterotropoides* Fr. Schmidt var. *Mandshuricum* (Maxim.) Kitag.), Madouling (*Aristolochia debilis* Sieb. et Zucc.) and Tianxianteng (*Aristolochia debilis* Sieb. et Zucc) retain medicinal standards in the Chinese Pharmacopoeia (Gao et al., 2017). However, the YHIS only had information on *Asari Radix*. According to the LC-MS method (Kuo et al., 2010), we determined that the content of aristolochic acid I (AAI) in *Asari Radix* was 0.869 μg/g. Some studies have reported that AA might induce the occurrence of HCC within one year (Lu et al., 2020). Thus, we defined our induction time as one year, and patients with HCC induction time less than one year after taking AA were excluded.

2.3. Diagnosis and follow-up of HCC

HCC was the primary outcome during the follow-up period. Diagnosis codes for HCC in ICD-10 included C22.0, D01.500 and D37.601, which complied with the management consensus guideline developed by the National Health Commission of the People's Republic of China (Ministry of Health of the People's Republic of China, 2020). HCC was diagnosed either by pathology or by clinical criteria. Patients were followed up from the index time until the diagnosis of HCC. The induction period of drug-induced HCC is more than one year, so we excluded patients diagnosed with HCC before the index date and within one year after the index date. We removed all HCC cases identified prior to January 1, 2010.

2.4. Statistical analysis

All statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). Continuous variables were presented as mean ± standard deviation (SD), and categorical variables were shown as numbers. Ninety-five percent confidence intervals (95% CI) were calculated using the exact formula. A P value < 0.05 was considered to indicate statistical significance.

3. Results

3.1. Baseline demographic features

Overall, our study identified 1 000 000 patients, aged over 18 years, between January 1, 2009, and November 12, 2018, in the database of YISH (Fig. 1). According to the exclusion criteria, a total of 182 648 patients were divided into the HBV cohort and the non-HBV cohort, including 49 500 HBV-infected and 1 33 148 non-HBV-infected patients, among whom 2 901 (5.86%) and 128 106 (3.79%) patients, respectively, had been taken *Asari Radix*. The demographic characteristics of these 182 648 patients were described in Table 1. The baseline characteristics showed higher proportions of patients with liver cirrhosis, alcohol-related disease, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, diabetes mellitus, or medication in the HBV cohort than in the non-HBV cohort.

3.2. Association of HCC with Asari Radix in HBV cohort

Among 49 500 HBV patients, 1 242 HCCs occurred during 480 892 person years of the follow-up (Table 2). A total of 46 599 patients were *Asari Radix* nonusers, while 2 901 patients were *Asari Radix* users in the HBV cohort. Among 1 242 patients who developed HCC, 1 201 patients were *Asari Radix* nonusers, whereas 41 patients were *Asari Radix* users. Among *Asari Radix* users, 24 (58.54%) HCC cases were discovered in 1 907 (65.74%) *Asari Radix* users taking 1–30 g dosage; 12 (29.27%) HCC cases were discovered in 344 (11.86%) *Asari Radix* users taking 31–60 g dosage; four (9.76%) HCC cases were found in 201 (6.93%) *Asari Radix* users taking 61–100 g dosage; one HCC case was detected in 274 (9.45%) *Asari Radix* users taking 101–200 g dosage. No HCC cases were found in 175 (6.03%) *Asari Radix* users taking over 200 g dosage. Concerning the cumulative dose of *Asari Radix*, there were no increasing trends in HCC incidence associated with doses from

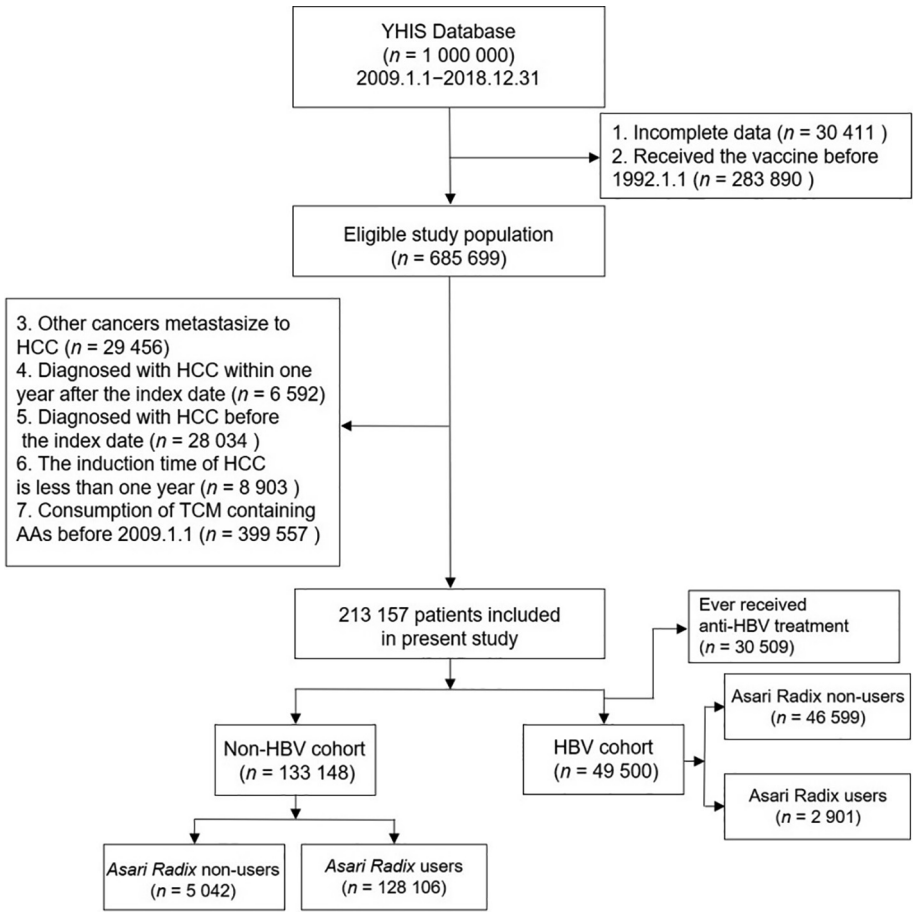

Fig. 1. Flow chart of study design.

none to >200 g in the HBV-infected cohort. Obviously, the incidence of HCC was lower among *Asari Radix* users (145.70 per 10^5) than among nonusers (265.43 per 10^5).

3.3. Association of HCC with Asari Radix in non-HBV cohort

In the non-HBV cohort, during 1 290 204 person-years of the follow-up, HCC occurred in 1 703 patients among 133 148 non-HBV-infected patients (Table 2). A total of 128 106 patients were *Asari Radix* nonusers, and 5 042 patients were *Asari Radix* users in the non-HBV cohort. Among 1 703 patients who developed HCC, 1 663 patients were *Asari Radix* nonusers, while 40 patients were *Asari Radix* users. Among *Asari Radix* users, 33 (82.50%) HCC cases were found in 3 862 (76.60%) *Asari Radix* users taking 1–30 g dosage; two (5.00%) HCC cases were found in 584 (11.58%) *Asari Radix* users taking 31–60 g dosage; two (5.00%) HCC cases were identified among 190 (3.77%) *Asari Radix* users taking 61–100 g dosage; and two (5.00%) HCC cases were discovered among 289 (5.73%) *Asari Radix* users taking 101–200 g dosage. Only one HCC case was found among 117 (2.32%) *Asari Radix* users taking over 200 g dosage. With regard to the cumulative dose of *Asari Radix*, there were no growing trends in the HCC incidence associated with doses from none to >200 g in the non-HBV-infected cohort. The occurrence of HCC among *Asari Radix* users (81.62 per 10^5) was significantly lower than that among nonusers (134.11 per 105).

None correlation observed between *Asari Radix* use and the development of HCC for both cohorts. *Asari Radix* taken <30 g was associated with a notably lower risk of hepatocarcinogenesis in the HBV cohort (HR, 0.49; 95% CI, 0.33–0.73) and in the non-HBV cohort (HR, 0.66; 95% CI, 0.46–0.93). The irrelevancy between *Asari Radix* taken in the dose range from 31 g to 200 g and the development of HCC was observed in both cohorts. Given that 90% of *Asari Radix* users consumed <201 g, we evaluated a maximum cumulative dose of 200 g, and the risk of HCC was not assessed for dosage above 200 g. Therefore, the dosage of maximum evaluated cumulative AA contained in *Asari Radix* that is not connected with the risk of developing HCC was 173.8 μg.

4. Discussion

In recent times, some researchers have reported that a positive correlation was observed between AAs and HCC (Li et al., 2020; Lu et al., 2020); however there were few of evidence to support the overview. We identified population-based studies assessing the relationship between AAs and HCC based on YISH database, in where, there was a very small amount of Madouling, Xungufeng, Tianxianteng, and Zhushalian. Meanwhile, of many Chinese patent medicine and herb medicine containing AAs, *Asari Radix* was the most widely used in YISH database. Hence, the purpose of our study was to assess the relevance between *Asari Radix* and HCC and determine the safe dosage of *Asari Radix*. Due to the principles of ethics in clinical research, a retrospective cohort study was adopted. The non-HBV cohort and the HBV cohort were defined to verify whether *Asari Radix* was an independent or a cooperative factor in HCC development. In this population-based retrospective cohort study, none correlation was observed between *Asari Radix* and hepatocarcinogenesis both in patients with and in those without HBV.

Table 1
Demographics and baseline characteristics of HBV-infected patients and non-HBV-infected patients.

Features	HBV cohort		*P* value	Non-HBV cohort		*P* value
	Asari Radix consumers (*n* = 2 901)	*Asari Radix* never consumers (*n* = 46 599)		*Asari Radix* consumers (*n* = 5 042)	*Asari Radix* never consumers (*n* = 128 106)	
Gender, *n* (%)			< 0.001			< 0.001
Male	1601 (55.19)	27,955 (59.99)		2435 (48.29)	68,101 (53.16)	
Female	1300 (44.81)	18,644 (40.01)		2607 (51.71)	60,005 (46.84)	
Age (years), *n* (%)			< 0.001			< 0.001
≤ 40	495 (17.06)	16,813 (36.08)		975 (19.34)	42,326 (33.04)	
> 40 and ≤ 49	759 (26.16)	11,668 (25.04)		1280 (25.39)	26,441 (20.64)	
> 50 and ≤ 59	771 (26.58)	9474 (20.33)		1269 (25.17)	25,352 (19.79)	
> 60 and ≤ 69	631 (21.75)	6114 (13.12)		914 (18.13)	19,485 (15.21)	
> 70, *n* (%)	245 (8.45)	2526 (5.43)		604 (11.97)	14,502 (11.32)	
Dosage of *Asari Radix*, *n* (%)						
Never		46,599			128,106	
1–30 g	1907 (65.74)			3862 (76.60)		
31–60 g	344 (11.86)			584 (11.58)		
61–100 g	201 (6.93)			190 (3.77)		
101–200 g	274 (9.45)			289 (5.73)		
> 200 g	175 (6.02)			117 (2.32)		
Liver Cirrhosis, *n* (%)			0.121			< 0.001
Yes	294 (10.13)	4321 (9.27)		81 (1.61)	1233 (0.96)	
No	2607 (89.87)	42,278 (90.73)		4961 (98.39)	126,873 (99.04)	
Alcohol-related disease, *n* (%)			0.165			0.345
Yes	51 (1.76)	671 (1.44)		7 (0.14)	121 (0.09)	
No	2850 (98.24)	45,928 (98.56)		5035 (99.86)	127,985 (99.91)	
Hypertension, *n* (%)			< 0.001			< 0.001
Yes	1783 (61.46)	11,309 (24.27)		2153 (42.70)	19,799 (15.46)	
No	1118 (38.54)	35,290 (75.73)		2889 (57.30)	108,307 (84.54)	
Hyerlipidemia, *n* (%)			< 0.001			< 0.001
Yes	1329 (45.81)	6854 (14.71)		1291 (25.60)	8512 (6.64)	
No	1572 (54.19)	39,745 (85.29)		3751 (74.40)	119,594 (93.36)	
Chronic obstructive pulmonary disease, *n* (%)			< 0.001			< 0.001
Yes	87 (3.00)	300 (0.64)		84 (1.67)	557 (0.43)	
No	2814 (97.00)	46,299 (99.36)		4958 (98.33)	127,549 (99.57)	
Diabetes Mellitus, *n* (%)			< 0.001			< 0.001
Yes	798 (27.51)	5455 (11.71)		746 (14.80)	7859 (6.13)	
No	2103 (72.49)	41,144 (88.29)		4296 (85.20)	120,247 (93.87)	
Medication, *n* (%)						
Anti-HBV treatments	1711 (58.98)	17,995 (38.62)	< 0.001	1452 (28.80)	9351 (7.30)	< 0.001
Aspirin	504 (17.37)	2778 (5.96)	< 0.001	449(8.91)	3852 (3.01)	< 0.001
NSAIDs	1952 (67.29)	10,951 (23.50)	< 0.001	2740(54.34)	21,028 (16.41)	< 0.001
Metformin	454 (15.65)	2068 (4.44)	< 0.001	392(7.77)	2838 (2.22)	< 0.001
ACE Inhibitors	526 (18.13)	1927 (4.14)	< 0.001	479(9.50)	2656 (2.07)	< 0.001
Statins	1161 (40.02)	5912 (12.69)	< 0.001	1139(22.59)	8074 (6.30)	< 0.001

Note: NSAIDs: non-steroidal anti-inflammatory drugs; ACE inhibitors: angiotensin-converting enzyme (ACE) inhibitor. *P* values were determined with the *t*-test, $P < 0.05$ indicates statistical significance.

The study results found out *Asari Radix* exposure was neither a direct nor indirect factor in the development of HCC, which are consistent with those reported in a Taiwanese study (Chen et al., 2019). In the non-HBV cohort, the incidence of HCC was 81.62 (per 10^5) and 134.11 (per 10^5) in *Asari Radix* users and nonusers. Obviously, the occurrence of HCC among *Asari Radix* users was lower than that in nonusers. There are several possible explanations. Firstly, we found that patients taking <30 g of *Asari Radix* accounted for 72.61% of all users. According to ancient literature, the recorded medical dosage did not exceed 3 g (Wang et al., 2018), which resulted in a lower cumulative induced dosage. The formation of DNA adducts may require a certain amount of AAs to induce significant A > T transversions in genes, however, the level of AAs in *Asari Radix* is overall lower (Liu et al., 2019; Sborchia et al., 2019; Stiborová et al., 2017). Second, since 1992, the Chinese government introduced HBV vaccination into routine immunization management (Sun & Hou, 2010); 95% coverage rate of HBV vaccination might have raised prejudice in HBV populations when exploring carcinogens (Cui & Zhuang, 2018). In addition, the induction time of liver cancer varies, which may be interrelate to the complex risk factors of liver cancer induction (El–Serag & Rudolph, 2007). A longer follow-up

Table 2
Crude and adjusted hazard rations between HBV cohorts and non-HBV cohorts.

Variables	Number of patients	Number of person-years	Number of patients with HCC	Incidence (per 10^5)	Crude HR	95% CI	*P* value
HBV cohort							
Total	49 500	480 892	1 242	258.27	–	–	–
Asari Radix dosage							
Never	46 599	452 476	1201	265.43	1.00	–	–
User total	2 901	28 140	41	145.70	0.55	0.40–0.75	< 0.001
1–30 g	1 907	18 479	24	129.88	0.49	0.33–0.73	0.001
30–60 g	344	3 329	12	360.47	1.36	0.77–2.40	0.291
61–100 g	201	1 947	4	205.44	0.77	0.29–2.07	0.609
101–200 g	274	2 655	1	37.66	0.14	0.02–1.01	0.051
> 201 g	175	1 699	0	0.00	–	–	–
Non-HBV cohort							
Total	133 148	1 290 204	1 703	131.99	–	–	–
Asari Radix dosage							
Never	128 106	1 240 066	1 663	134.11	1.00	–	–
User total	5 042	49 008	40	81.62	0.61	0.44–0.83	0.002
1–30 g	3 862	37 538	33	87.91	0.66	0.46–0.93	0.016
30–60 g	584	5 670	2	35.27	0.26	0.07–1.05	0.059
61–100 g	190	1 841	2	108.64	0.81	0.20–3.24	0.766
101–200 g	289	2 806	2	71.28	0.53	0.13–2.13	0.372
> 201 g	117	1 133	1	88.26	0.66	0.09–4.68	0.676

Note: CI, confidence interval; HR, hazard ratio. *P* values were determined with the *t*-test, $P < 0.05$ indicates statistical significance.

period may be necessary to assess the definite relationship between *Asari Radix* and HCC.

Meanwhile, *Asari Radix* did not play a cooperative role in HCC patients with HBV. In HBV cohort, the occurrence of HCC was not relatively higher in patients with *Asari Radix* use than nonusers, which suggesting that *Asari Radix* had no collaborative part in the development of HCC. Interestingly, Chen et al. took contrary positions; AAs may increase the risk of HCC in HBV-positive populations (Chen et al., 2018). The increased risk observed in the analysis might be associated with a subgroup of those with more severe liver hepatitis, who are more likely to develop liver cancer (Chen et al., 2018; Chen et al., 2019). However, patients diagnosed liver disease were less than none hepatopathy in our subgroup data.

There are some limitations of our study. First, due to the small amount of *Asari Radix*, the outcome of HCC after high-dose use of *Asari Radix* cannot be inferred. Second, poor compliance with treatment in practical situation leads to overestimation of the cumulative AA dosage. Third, the cumulative AAI dosage may be underestimated. For example, many Chinese medicines can be purchased through convenient online shopping services; however, healthy products containing AA were not included in the management of medication records (Gao et al, 2017). Innocuous herbs can be displaced by herbs carrying high concentrations of AAs (Feng et al., 2018). Fourth, some confounding factors related to HCC, including body mass index, smoking, alcohol intake, and exposure to aflatoxin B1, were not included in our study. Finally, because data desensitization was impossible, alcohol-related diseases, non-alcoholic steatohepatitis, hypertension, hyperlipidemia, and chronic obstructive pulmonary disease were shown as relevant additional covariates, but no further sensitivity analysis of these covariates was available to eliminate the confounding factors.

5. Conclusion

The present study demonstrated that *Asari Radix* consumption did not increase the risk of HCC among HBV or non-HBV patients in a real-world scenario in mainland China. Because of biases and unmeasured confounding factors, these conclusions should be interpreted with caution, and experimental confirmations are needed. Further prospective multicenter studies are needed to confirm the association.

Editor Note

Xiaohe Xiao is Editorial Board Members of Chinese Herbal Medicines. He was blinded from reviewing or making decisions on the manuscript. The article was subject to the journal's standard procedures, with peer review handled independently of this Editorial Board Member and their research groups.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Cao, C., Wang, J. Z., Wang, L., Shang, M. Y., Liu, G. X., Xu, F., ... Cai, S. Q. (2015). Simultaneous determination of seven principal constituents in *Asari Radix et Rhizoma* by HPLC. *Journal of Chinese Pharmaceutical Sciences, 24*(8), 530–537.

Chen, C. J., Yang, Y. H., Lin, M. H., Lee, C. P., Tsan, Y. T., Lai, M. N., ... Chen, P. C. (2019). Herbal medicine containing aristolochic acid and the risk of primary liver cancer in patients with hepatitis C virus infection. *Cancer Epidemiology, Biomarkers & Prevention, 28*(11), 1876–1883.

Chen, C. J., Yang, Y. H., Lin, M. H., Lee, C. P., Tsan, Y. T., Lai, M. N., ... Health Data Analysis in Taiwan (hDATa) Research Group (2018). Herbal medicine containing aristolochic acid and the risk of hepatocellular carcinoma in patients with hepatitis B virus infection. *International Journal of Cancer, 143*(7), 1578–1587.

Chen, C. N., Tsai, Y. T., & Lai, J. N. (2019). 8 years post-marketing surveillance between *Asari Radix* and hepatocellular carcinoma: Nationwide population-based evidence against an association. *Journal of Ethnopharmacology, 243*(2019), 112094.

Chiang, S. Y., Lee, P. Y., Lai, M. T., Shen, L. C., Chung, W. S., Huang, H. F., ... Wu, H. C. (2011). Safrole-2′,3′-oxide induces cytotoxic and genotoxic effects in HepG2 cells and in mice. *Mutation Research, 726*(2), 234–241.

Cui, F. Q., & Zhuang, H. (2018). Epidemics and control of hepatitis B in China. *Chinese Journal of Viral Diseases, 4*(8), 257–264.

El–Serag, H. B., & Rudolph, K. L. (2007). Hepatocellular carcinoma: Epidemiology and molecular carcinogenesis. *Gastroenterology, 132*(7), 2557–2576.

Feng, X., Fang, S. N., Gao, Y. X., Liu, J. P., & Chen, W. (2018). Current research situation of nephrotoxicity of Chinese herbal medicine. *China Journal of Chinese Materia Medica, 43*(03), 417–424.

Gao, Y., Xiao, X. H., Zhu, X. X., Liang, A. H., & Zhang, B. L. (2017). Study and opinion on toxicity of aristolochic acid. *China Journal of Chinese Materia Medica, 42*(21), 4049–4053.

Grollman, A. P., & Marcus, D. M. (2016). Global hazards of herbal remedies: Lessons from *Aristolochia*: The lesson from the health hazards of *Aristolochia* should lead to more research into the safety and efficacy of medicinal plants. *EMBO Reports, 17*(5), 619–625.

Ji, X., Feng, G., Chen, G., & Shi, T. (2018). Lack of correlation between aristolochic acid exposure and hepatocellular carcinoma. *Science China Life Sciences, 61*(6), 727–728.

Kim, J. H., Kim, Y. D., Lee, M., Jun, B. G., Kim, T. S., Suk, K. T., ... Choi, D. H. (2018). Modified PAGE-B score predicts the risk of hepatocellular carcinoma in Asians with chronic hepatitis B on antiviral therapy. *Journal of Hepatology, 69*(5), 1066–1073.

Kuo, C. H., Lee, C. W., Lin, S. C., Tsai, I. L., Lee, S. S., Tseng, Y. J., ... Wu, L. (2010). Rapid determination of aristolochic acids I and II in herbal products and biological samples by ultra-high-pressure liquid chromatography-tandem mass spectrometry. *Talanta, 80*(5), 1672–1680.

Li, H., Lin, H., Zhao, H., Xu, Y., Cheng, Y., Shen, P., & Zhan, S. (2018). Statins use and risk of new-onset diabetes in hypertensive patients: A population-based retrospective cohort study in Yinzhou district, Ningbo city, People's Republic of China. *Therapeutics and Clinical Risk Management, 14*, 823–832.

Li, Y., Zhu, S., Xue, M., Jing, Y., Liu, X., Cai, D., ... Zhang, L. (2020). Aristolochic acid I promotes the invasion and migration of hepatocellular carcinoma cells by activating the C3a/C3aR complement system. *Toxicology Letter, S0378–4274*(20), 30410.

Liu, S., Xian, Z., Zhao, Y., Wang, L., Tian, J., Pan, C., ... Liang, A. (2021). Quantitative determination and toxicity evaluation of aristolochic acid analogues in *Asarum heterotropoides* F. Schmidt (Xixin) and traditional Chinese patent medicines. *Frontiers in Pharmacology, 12*, 761593.

Liu, Y., Chan, C. K., Jin, L., Wong, S. K., & Chan, W. (2019). Quantitation of DNA adducts in target and nontarget organs of aristolochic acid I-exposed rats: Correlating DNA adduct levels with organotropic activities. *Chemical Research in Toxicology, 32*(3), 397–399.

Liu, Y. Z., Lu, H. L., Qi, X. M., Xing, G. Z., Wang, X., Yu, P., ... Ren, J. (2021). Aristolochic acid I promoted clonal expansion but did not induce hepatocellular carcinoma in adult rats. *Acta Pharmacologica Sinica, 42*(12), 2094–2105.

Lu, Z. N., Luo, Q., Zhao, L. N., Shi, Y., Wang, N., Wang, L., & Han, Z. G. (2020). The mutational features of aristolochic acid-induced mouse and human liver cancers. *Hepatology, 71*(3), 929–942.

Ministry of Health of the People's Republic of China (2020). Updated standards for the diagnosis and treatment of primary liver cancer. *Chinese Journal of Hepatology, 33*(6), 112–128.

Nault, J. C., & Letouzé, E. (2019). Mutational processes in hepatocellular carcinoma: The story of aristolochic acid. *Seminars in Liver Disease, 39*, 334–340.

Ng, A., Poon, S. L., Huang, M. N., Lim, J. Q., Boot, A., Yu, W., ... Rozen, S. G. (2017). Aristolochic acids and their derivatives are widely implicated in liver cancers in Taiwan and throughout Asia. *Science Translational Medicine, 9*(412), eaan6446.

Owusu Sekyere, S., Schlevogt, B., Mettke, F., Kabbani, M., Deterding, K., Wirth, T. C., ... Wedemeyer, H. (2019). HCC immune surveillance and antiviral therapy of hepatitis C virus infection. *Liver Cancer, 8*(1), 41–65.

Pharmacopoeia Commission of the People's Republic of China (2020). *Pharmacopoeia of the People's Republic of China, vol 1*, 240.

Sborchia, M., Keun, H. C., Phillips, D. H., & Arlt, V. M. (2019). The impact of p53 on aristolochic acid I-induced gene expression *in vivo*. *International Journal of Molecular Sciences, 20*(24), 6155.

Stiborová, M., Arlt, V. M., & Schmeiser, H. H. (2017). DNA adducts formed by aristolochic acid are unique biomarkers of exposure and explain the initiation phase of upper urothelial cancer. *International Journal of Molecular Sciences, 18*(10), 2144.

Sun, J., & Hou, J. L. (2010). Management of chronic hepatitis B: Experience from China. *Journal of Viral Hepatitis, 17*, 10–17.

Wang, L., Wu, B., & Wang, S. Y. (2018). Correctly understand "Asarum is no more than 3 gram". *Journal of Tianjin University of Traditional Chinese Medicine, 5*(37), 366–368.

Wen, H., Gao, H. Y., Qi, W., Xiao, F., Wang, L. L., Wang, D., & Yuan, D. (2014). Simultaneous determination of twenty-two components in *Asari Radix* et *Rhizoma* by ultra performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry. *Planta Medica, 80*(18), 1753–1762.

Yang, A. H., Zhang, L., Zhi, D. X., Liu, W. L., Gao, X., & He, X. (2018). Identification and analysis of the reactive metabolites related to the hepatotoxicity of safrole. *Xenobiotica, 48*(11), 1164–1172.

Zhao, Z. Z., Liang, Z. T., Jiang, Z. H., Leung, K. S., Chan, C. L., Chan, H. Y., ... Law, K. W. (2008). Comparative study on the aristolochic acid I content of herba Asari for safe use. *Phytomedicine, 15*(9), 741–748.