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

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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 105). 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 105). 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.

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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 (YHS) in Ningbo City, Zhejiang Province, People's Republic of China, between January 1, 2009, and December 12, 2018. The YHS 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 manshurensis 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 YHS 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%) HCC cases were found in 201 (6.93%) 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...
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 (265.43 per 10^5).

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.
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

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**Table 1**

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

| Features                        | HBV cohort | Non-HBV cohort |
|---------------------------------|------------|----------------|
|                                 | 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 (%)                   |            |                |            |                |
| Male                            | 1,601 (55.19) | 27,955 (59.99) | 2,435 (48.29) | 68,101 (53.16) |
| Female                          | 1,300 (44.81) | 18,644 (40.01) | 2,607 (51.71) | 60,005 (46.84) |
| Age (years), n (%)              |            |                |            |                |
| ≤ 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) | 1,280 (25.39) | 26,441 (20.64) |
| > 50 and ≤ 59                   | 771 (26.58) | 9,474 (20.33) | 1,269 (25.17) | 25,352 (19.79) |
| > 60 and ≤ 69                   | 631 (21.75) | 6,114 (13.12) | 914 (18.13) | 19,485 (15.21) |
| > 70, n (%)                     | 245 (8.45) | 2,526 (5.43) | 604 (11.97) | 14,502 (11.32) |
| Dosage of Asari Radix, n (%)    |            |                |            |                |
| Never                           | 1,907 (65.74) | 3,862 (76.60) | 2,153 (42.70) | 19,799 (15.46) |
| 1–30 g                          | 344 (11.86) | 584 (11.58) | 7 (0.14) | 121 (0.09) |
| 31–60 g                         | 201 (6.93) | 190 (3.77) | 5035 (99.86) | 127,985 (99.91) |
| 61–100 g                        | 274 (9.45) | 289 (5.73) | 1280 (25.39) | 25,352 (19.79) |
| 101–200 g                       | 175 (6.02) | 117 (2.32) | 914 (18.13) | 19,485 (15.21) |
| Liver Cirrhosis, n (%)          |            |                |            |                |
| Yes                             | 2,94 (12.13) | 4,227 (90.73) | 81 (1.61) | 1233 (0.96) |
| No                              | 2,607 (89.87) | 4,496 (98.39) | 1,233 (23.94) | 126,873 (99.04) |
| Alcohol-related disease, n (%)  |            |                |            |                |
| Yes                             | 51 (1.76) | 671 (1.44) | 7 (0.14) | 121 (0.09) |
| No                              | 2,850 (98.24) | 4,952 (98.56) | 5035 (99.86) | 127,985 (99.91) |
| Hypertension, n (%)             |            |                |            |                |
| Yes                             | 1,783 (61.46) | 11,309 (24.27) | 2,153 (42.70) | 19,799 (15.46) |
| No                              | 1,118 (38.54) | 35,290 (75.73) | 2,889 (57.30) | 108,307 (84.54) |
| Hyperlipidemia, n (%)           |            |                |            |                |
| Yes                             | 1,329 (45.81) | 6,854 (14.71) | 1,291 (25.60) | 8512 (6.64) |
| No                              | 1,572 (54.19) | 39,745 (85.29) | 3,751 (74.40) | 119,594 (93.36) |
| Chronic obstructive pulmonary disease, n (%) |            |                |            |                |
| Yes                             | 87 (3.00) | 300 (0.64) | 84 (1.67) | 557 (0.43) |
| No                              | 2,814 (97.00) | 46,299 (99.36) | 4,958 (98.33) | 127,549 (99.57) |
| Diabetes Mellitus, n (%)        |            |                |            |                |
| Yes                             | 798 (27.51) | 5,455 (11.71) | 746 (14.80) | 7,859 (6.13) |
| No                              | 2,103 (72.49) | 41,144 (88.29) | 4,296 (85.20) | 120,247 (93.87) |
| Medication, n (%)               |            |                |            |                |
| Anti-HBV treatments             | 1,711 (58.98) | 17,995 (38.62) | 1,452 (28.80) | 9,351 (7.30) |
| Aspirin                         | 504 (17.37) | 2,778 (5.96) | 449 (8.91) | 3,852 (3.01) |
| NSAIDs                          | 1,952 (67.29) | 10,951 (23.50) | 2,740 (54.34) | 21,028 (16.41) |
| Metformin                       | 454 (15.65) | 2,068 (4.44) | 392 (7.77) | 2,838 (2.22) |
| ACE Inhibitors                  | 526 (18.13) | 1,927 (4.14) | 479 (9.50) | 2,656 (2.07) |
| Statins                         | 1,161 (40.02) | 5,912 (12.69) | 1,139 (22.59) | 8,074 (6.30) |

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.
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. 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.

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 10^3) | 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                | 1 201                      | 265.43               | 1.00     | 0.40–0.75    | < 0.001 |
| 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.

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.
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