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Does herbal medicine reduce the risk of hepatocellular carcinoma?

Yasushi Rino, Norio Yukawa, Naoto Yamamoto

Yasushi Rino, Norio Yukawa, Naoto Yamamoto, Department of Surgery, School of Medicine, Yokohama City University, Yokohama 236-0004, Japan

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Correspondence to: Yasushi Rino, MD, Department of Surgery, School of Medicine, Yokohama City University, 3-9, Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan. rino@med.yokohama-cu.ac.jp
 Telephone: +81-45-7872645
 Fax: +81-45-7860226

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Abstract

Many herbal medicines are effective anti-inflammatory agents and may therefore suppress the development of hepatocellular carcinoma (HCC). Recently, treatment with a single-tablet regimen containing ledipasvir and

sofosbuvir resulted in high rates of sustained virologic response among patients with hepatitis C virus genotype 1 infection who did not respond to prior interferon-based treatment. Patients with chronic hepatitis C are expected to receive this treatment worldwide. However, many patients have hepatitis-like fatty liver and nonalcoholic steatohepatitis. A strategy to prevent the development of HCC in this subgroup of patients is urgently required. Whether herbal medicines can suppress the development of HCC remains to be established. However, herbal medicines are effective anti-inflammatory agents and may inhibit the development of HCC. Clinical trials exploring the effectiveness of herbal medicines in the prevention and treatment of HCC are therefore warranted. The current lack of knowledge and of educational programs is a barrier to increasing the use of potentially effective herbal medicines and performing prospective clinical trials.

Key words: Herbal medicine; Hepatocellular carcinoma; Anti-inflammatory; Hepatocellular carcinoma prevention; Chronic hepatitis

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Core tip: Many herbal medicines are effective anti-inflammatory agents and may suppress the development of hepatocellular carcinoma (HCC). Patients with chronic hepatitis C generally receive ledipasvir and sofosbuvir worldwide. However, many patients have hepatitis-like fatty liver and nonalcoholic steatohepatitis. A strategy to prevent the development of HCC is urgently required for this subgroup of patients. Future research needs to explore the effectiveness of herbal medicines in preventing and treating HCC. The current lack of knowledge and of educational programs is a barrier to increasing the use of potentially effective herbal medicines and performing prospective clinical trials.

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INTRODUCTION

Many clinical studies have shown that continuous inflammation is related to the pathogenesis of gastric cancer^[1], colorectal cancer^[2], and cholangiocellular carcinoma^[3,4]. A relation between hepatitis C virus (HCV)-associated liver cirrhosis (LC) and hepatocellular carcinoma (HCC) has also been reported^[5]. Miyakawa *et al.*^[6] found that continuously elevated serum alanine aminotransferase (ALT) levels are related to a marked increase in the risk of HCC. Genetic alterations most likely accumulate rapidly in the presence of persistent inflammation, and the multistep process of carcinogenesis or promotion of tumor growth is thought to progress more rapidly in patients with continuously high ALT levels. Herbal medicines with anti-inflammatory activity have been suggested to prevent the development of HCC^[7]. In this report, we review whether herbal medicines are effective anti-inflammatory agents that can potentially suppress the development of HCC.

HCC AND HCV-ASSOCIATED LC

The importance of hepatocytic necrosis in the recurrence of HCC after hepatectomy has been demonstrated in patients with HCV-associated LC and HCC, and suppression of the hepatic necroinflammatory process has been suggested to have an important role in preventing HCC recurrence^[8]. Accelerated recurrence of HCC has been shown to be related to high serum ALT levels in patients with HCV-associated LC^[9]. Moreover, the development of HCC is more rapid in the presence of high serum ALT levels in patients with HCV-associated LC^[10]. Multicentric hepatocarcinogenesis strongly correlates with sustained necroinflammation of the liver in patients with early-stage HCV-associated LC^[11]. Sustained alleviation of inflammation, as indicated by low serum ALT levels, provides a survival advantage mainly attributed to the longer non-recurrence interval and possibly fewer recurrences after hepatectomy in HCC patients with HCV-associated LC^[12]. Persistently high ALT levels for 3 successive years after the diagnosis of LC can be predictive of a very high incidence of HCC in patients with Child A HCV-associated LC^[6], and a serum ALT level of 80 IU was adopted as a cut-off value^[8]. Previous studies have suggested that alleviation of inflammation by anti-inflammatory drugs may prolong the recurrence-free interval and decrease the risk of HCC in patients with HCV-associated LC. In 2006, we reported that herbal medicine effectively

reduces serum ALT levels^[7]. In that study, we analyzed outcomes in patients with HCV-LC who received therapy to reduce ALT levels, with the ultimate goal of finding a way to prevent the development of HCC from HCV-LC. A total of 74 consecutive patients with Child stage A HCV-LC were followed-up for > 10 years to assess the development of HCC. They were divided into two groups: the aggressive treatment group, which received aggressive ALT reduction therapy, and the non-aggressive treatment group, which did not receive aggressive ALT reduction therapy. The patients were then subdivided into 3 sub-groups according to whether their serum ALT levels were high, low, or unclassifiable. In the aggressive treatment group and the non-aggressive treatment group, the high ALT group respectively comprised 9 and 5 patients whose annual mean serum ALT levels were persistently high (≥ 80 IU), and the low ALT group respectively comprised 19 and 20 patients whose annual mean serum ALT levels were persistently low (< 80 IU). The other 11 patients in the aggressive treatment group and 10 patients in the non-aggressive treatment group had fluctuating annual mean serum ALT levels that were unclassifiable (unclassified group). In the non-aggressive treatment group, HCC developed in 65.7% of the patients within 13 years, in contrast to only 41.0% in the aggressive treatment group ($P = 0.039$). The median time to HCC development was 12.8 years in the aggressive treatment group, as compared with only 3.8 years in the non-aggressive treatment group ($P = 0.0013$). Multivariate analysis demonstrated that the mode of reduction therapy and ALT levels were significantly related to the development of HCC. The chances of surviving for more than 10 years without developing HCC in these patients with Child stage A HCV-LC were far better in the aggressive treatment group than in the non-aggressive treatment group. These results suggested that aggressive therapy to reduce ALT levels in patients with HCV-LC can significantly prevent the development of HCC. The herbal medicines used for aggressive reduction therapy were sho-saiko-to, juzen-taiho-to, and Stronger-Neo Minophagen C (SNMC, glycyrrhizin)^[7].

HERBAL MEDICINES

Sho-saiko-to

Sho-saiko-to is a herbal medicine used in Japan to treat chronic viral liver diseases. It acts by reducing inflammatory processes and controlling ALT levels^[13]. Sho-saiko-to did not significantly improve liver fibrosis and related laboratory data irrespective of ALT levels in patients with chronic hepatitis C^[14]. Some studies have suggested that sho-saiko-to has no effect on liver dysfunction. However, most studies have reported that sho-saiko-to is an effective anti-inflammatory agent. Bupleurum is one of the ingredients of sho-saiko-to. Saikosaponin-A (SSA) and Saikosaponin-D (SSD) are extracted from bupleurum. SSA is an

Table 1 Herbal medicines and their effects

| Medicine | Target | Anti-inflammation | HCC |
|----------------|--------------------------------|-------------------|---------------------------|
| Sho-saiko-to | COX2↓ | Effective | Risk reduction? |
| Juzen-taiho-to | NKT↑ | Effective | Risk reduction? |
| SNMC | MIP-1α↓ TNF-1α↓ | Effective | Risk reduction? |
| Baicalein | | | Apoptosis? |
| Ginsenoside | Bcl-2 family proteins MMP-1 | | Prevention of metastasis? |

Baicalein is a component of sho-saiko-to. Ginsenoside is a component of sho-saiko-to and juzen-taiho-to. HCC: Hepatocellular carcinoma; SNMC: Stronger-Neo Minophagen C; COX2: Cyclooxygenase-2; NKT: Natural killer T cell; MIP-1α: Macrophage inflammatory protein-1α; TNF-1α: Tumor necrosis factor-1α; MMP-1: Matrix metalloproteinase-1.

antioxidant. Hepatic proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6, were significantly inhibited, and anti-inflammatory cytokine IL-10 was significantly increased by SSA. SSA suppresses inflammation and fibrogenesis^[15]. Sho-saiko-to has been reported to be effective for LC or chronic hepatitis. Pretreatment with SSD markedly inhibits acute hepatic injury induced by carbon tetrachloride (CCl₄)^[16]. Cyclooxygenase-2 (COX-2) and CCAAT/enhancer binding protein β (C/EBPβ) have been shown to participate in inflammation and carcinogenesis, are co-overexpressed in human HCC tissue and are positively correlated with each other. SSD prevents diethyl-nitrosamine-induced HCC in rats by inhibiting C/EBPβ and COX-2^[17]. SSD treatment inhibited signal transducer and activator of transcription 3 (STAT3) activation, reduced the protein level of hypoxia-inducible factor-1 alpha (HIF-1α), and decreased the expression of COX-2. SSD may target HCC cells by suppressing the expression of COX-2 through the phosphor-STAT3/HIF-1α pathway in HCC^[18]. SSA inhibited the growth and DNA synthesis of HCC cell lines. Sho-saiko-to includes potent antitumor components, such as SSA^[19]. Sho-saiko-to is considered an effective anti-inflammatory agent that suppresses the development of HCC by inhibiting COX-2 (Table 1).

Juzen-taiho-to

Juzen-taiho-to was found to increase the secretion of interferon-γ (INF-γ) as well as IL-4, IL-5, and IL-6 from stimulated hepatic lymphocytes, whereas IL-2 secretion was reduced. Modulation of cytokine secretion by juzen-taiho-to might not result from changes in the number of cytokine-secreting cells within hepatic lymphocytes. The CD4/CD8 ratio and αβ/γδ T-cell receptor (TCR) ratio in hepatic lymphocytes were unchanged. However, flow cytometric analysis revealed that the population of CD3-positive intermediate cells among natural killer-positive cells (natural killer T cells, NKT cells) increased after oral administration of juzen-

taiho-to. Juzen-taiho-to enhanced transcription of IL-12 mRNA in the liver. A rise in the NKT cell population contributes, at least partially, to the modulating effect of juzen-taiho-to on cytokine production in hepatic lymphocytes and macrophages. The production of IL-12 in liver may also contribute to the induction of NKT cells^[20]. Juzen-taiho-to is thus considered to suppress hepatic inflammation and induce NKT cells. On the other hand, some authors have reported that juzen-taiho-to does not improve liver dysfunction for the following reasons: The preventive effect of juzen-taiho-to on hyperammonemia occurring after partial hepatectomy was examined. Pre-surgical treatment with juzen-taiho-to was found to significantly suppress this post-surgical hyperammonemia. However, juzen-taiho-to did not improve post-surgical liver dysfunction. Juzen-taiho-to administration stabilized the intestinal microbiota and maintained the pre-surgical microbial environment of the gut^[21]. Juzen-taiho-to was thus suggested to be ineffective for liver dysfunction. On the other hand, sho-saiko-to and juzen-taiho-to inhibited necroinflammation and fibrosis in the liver of a mouse model of nonalcoholic steatohepatitis (NASH), although the underlying mechanisms were not fully elucidated^[22]. Overall, juzen-taiho-to appears to be an effective anti-inflammatory agent that induces NKT cells (Table 1).

SNMC, glycyrrhizin

SNMC is a herbal medicine used in Japan to treat chronic viral liver diseases. It acts by reducing inflammatory processes and controlling ALT levels^[23]. Historical sources for the use of glycyrrhizin species include ancient manuscripts from China, India, and Greece. They all mention its use for symptoms of viral respiratory tract infections and hepatitis^[24]. Moreover, a preparation of glycyrrhizin combined with glycine and cysteine (SNMC) has been widely and successfully used in Japan as an antihepatitis drug, although its mechanism of pharmacological action was unclear as of 1982^[25]. Recently, its mechanism of pharmacological action was reported. 18β-glycyrrhetic acid (GA) reduced macrophage inflammatory protein (MIP)-1α expression on Kupffer cells by down-regulating MyDD88 expression and inhibiting NF-κB activation. GA exerts anti-inflammatory activity by inhibiting MIP-1α^[26]. CCl₄ induced liver injury and markedly increased the level of circulating TNF-α in mice, which was reduced by glycyrrhizin. The levels of hepatic inducible nitric oxide (NO) synthase, COX-2, and heme oxygenase-1 protein expression were markedly higher after CCl₄ treatment. Glycyrrhizin diminished the increases in inducible NO and COX-2, but further augmented the protein expression of heme oxygenase-1. Glycyrrhizin alleviates CCl₄-induced liver injury, and this protection is most likely due to the induction of heme oxygenase-1 and the down-regulation of proinflammatory mediators^[27].

In mice with ConA-induced hepatitis, the production of IL-6 and IL-10 was enhanced by diammonium glycyrrhizinate (DG), which is extracted and purified from *Radix glycyrrhizae*. DG may protect the liver from injury *via* two pathways: direct protection of hepatocytes from apoptosis through an IL-6-dependent pathway and indirect suppression of T-cell-mediated inflammation through an IL-10-dependent pathway^[28]. On the basis of clinical and histological markers, it was concluded that SNMC can suppress liver necrosis and inflammation in patients with chronic hepatitis C, suggesting that long-term treatment with the product might be useful for preventing liver cirrhosis and HCC^[7,29]. SNMC is considered an effective anti-inflammatory agent that suppresses COX-2 mRNA expression (Table 1).

Other herbal medicines

Baicalein and baicalin may have beneficial effects on the development of hepatic steatosis and fibrosis^[30-33]. In addition, flavonoids from *Scutellaria baicalensis* Georgi (baicalein, baicalin, and wogonin) dose-dependently decreased HCC cell viability in association with the collapse of mitochondrial membrane potential and the depletion of glutathione content. These flavonoids resulted in a prominent increase in the G2/M population in one HCC cell line, whereas an accumulation of the sub-G1 (hypoploid) peak was observed in another HCC cell line. In other cell lines, baicalein and baicalin dramatically boosted the hypoploid peak, whereas wogonin mainly affected G1 phase accumulation. Baicalein, baicalin, and wogonin might be effective candidates for inducing apoptosis or inhibiting proliferation in various human HCC cell lines^[34]. Baicalein is a component of sho-saiko-to.

Ginsenoside inhibited tumor growth *in vivo* and prolonged mouse survival time by inducing HCC cell apoptosis *via* an intrinsic pathway by altering Bcl-2 family proteins^[35]. Ginsenoside suppresses matrix metalloproteinase-1 (MMP-1) expression by inhibiting activator protein-1 and the mitogen-activated protein kinase signaling pathway in human HCC cells. Therefore, ginsenoside has potential for the development of novel chemotherapeutic agents for the treatment and prevention of metastasis from HCC related to MMP-1 expression^[36,37]. Ginsenoside is a component of sho-saiko-to and juzu-taiho-to (Table 1).

CONCLUSION

Although there are some negative opinions^[14,19], herbal medicines are considered effective anti-inflammatory agents, which could potentially suppress the development of HCC. Currently available evidence indicates that prospective controlled studies of herbal medicines in patients with chronic hepatitis C are warranted.

Recently, treatment with a once-daily, fixed-dose

combination tablet containing ledipasvir and sofosbuvir resulted in high rates of sustained virologic response among patients with HCV genotype 1 infection who had not responded to prior interferon-based treatment^[38]. Patients with chronic hepatitis C in all countries will generally receive this treatment. However, many patients have hepatitis-like fatty liver and NASH. To date, the prevalence of NASH in the general population has not been clearly defined. An autopsy study from the late 1980s estimated that the prevalence of NASH was 2.7% among lean individuals, rising to 18.5% among markedly obese patients. More recently, a study evaluating donor livers before transplantation found that the prevalence of NASH ranged from 1.1% to 14%^[39]. A strategy to prevent the development of HCC in such patients is urgently required.

A national survey evaluating oncologists' knowledge, attitudes, and practice patterns regarding herb and supplement use by patients with cancer in the United States was reported in December 2014. Oncologists discussed the use of herbs and supplements with 41% of their patients. Two of three oncologists indicated they did not have enough knowledge to respond to questions from patients regarding herbs and supplements, and 59% had not received any education about herbs or supplements^[40].

Evidence to show that herbal medicines can suppress the development of HCC remains to be established. However, herbal medicines are effective anti-inflammatory agents and may suppress the development of HCC. Clinical trials exploring the effectiveness of herbal medicines in the prevention and treatment of HCC are therefore warranted. The current lack of knowledge and of educational programs is a barrier to increasing the use of potentially effective herbal medicines and performing prospective clinical trials.

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