



Prevalence and predictors of complementary and alternative medicine modalities in patients with chronic hepatitis B

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Abstract

Background & Aims: The use of complementary and alternative medicine (CAM) in patients with chronic hepatitis B (CHB) can interact with antiviral treatment or influence health-seeking behaviour. We aimed to study the use of individual CAM modalities in CHB and explore determinants of use, particularly migration-related, socio-economic and clinical factors.

Methods: A total of 436 CHB outpatients who attended the Toronto Centre for Liver Disease in 2015-2016 were included in this cross-sectional study. Using the comprehensive I-CAM questionnaire and health records, data were collected on socio-demographic and clinical variables and on usage of 16 CAM modalities in the last year.

Results: Sixty percent of patients were male, 74% were Asian and 46% were using antiviral treatment. Three-hundred and nine (71%) patients used CAM. Vitamin/mineral preparations (45% of patients) were most commonly used. Overall CAM use and the specific use of potentially injurious CAM, such as green tea extract (9.2%) and St. John's wort (0.2%), were not associated with liver disease severity. Female sex, family history of CHB, lower serum HBV DNA, and higher socio-economic status were independently associated with bio-holistic CAM use, the clinically most-relevant CAM group ($P < 0.05$); ethnicity, antiviral therapy use and liver disease severity were not.

Conclusions: CAM use among CHB patients was extensive, especially use of vitamin and mineral preparations, but without direct influence on liver disease severity. Bio-holistic CAM use appeared to be associated with socio-economic status rather than with ethnicity or liver disease severity. Despite the rare use of hepatotoxins, physicians should actively inquire about it.

KEYWORDS

chronic hepatitis B, complementary and alternative medicine, ethnicity, hepatotoxicity

Abbreviations: ALT, alanine aminotransferase; CAM, complementary and alternative medicine; CHB, chronic hepatitis B; CI, confidence interval; HBeAg, Hepatitis B e Antigen; HBsAg, Hepatitis B surface Antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; I-CAM-Q, International Questionnaire to Measure Use of Complementary and Alternative Medicine; NA, nucleos(t)ide analogue; ns, not significant; OR, odds ratio; PEG, pegylated; SD, standard deviation.

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1 | INTRODUCTION

Chronic hepatitis B (CHB) affects approximately 240 million people worldwide and the associated liver-related morbidity and mortality continue to rise.¹⁻³ Global migration is changing the epidemiology of CHB, especially in low-endemic regions (North-America, Europe) with a high immigration rate from highly endemic areas.^{4,5} These epidemiological shifts increase the ethno-cultural diversity, and could therefore influence the use of and perceptions on conventional Western medicine and on complementary and alternative medicine (CAM).

Patients with chronic diseases increasingly use CAM in addition to, or as a replacement of conventional treatments.⁶ CAM is defined as 'a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine'.⁷ Examples of CAM include Traditional Chinese Medicine, acupuncture and dietary supplements. The proportion of patients with chronic liver disease who use CAM varies widely from 27% to 80%.⁸⁻¹¹ Patients use CAM both for disease-related symptoms as well as for general well-being.⁶ The identification of patterns in CAM use could be of great relevance to health care providers, since CAM products may interact with antiviral treatment or influence the health care-seeking behaviour of patients.^{12,13} Insight into CAM use is especially important for an ethnically diverse population such as those with CHB, where ethnic and acculturation factors can enlarge differences in CAM use and clinical outcomes.

The prevalence and predictors of individual CAM modalities in patients with CHB have not been well characterized. Previous studies on CAM use in CHB focused on specific types of CAM, were restricted to subgroups of patients, or evaluated few clinically important determinants.^{9,14,15} We evaluated the use of various CAM modalities and its relation to clinical, socio-economic and migration-related factors in a large, multi-ethnic CHB cohort.

2 | PATIENTS AND METHODS

2.1 | Study population

Patients with CHB aged 18 years or above who attended the hepatology outpatient clinic of the Toronto Centre for Liver Disease, Canada, between January 1, 2015 and October 31, 2016 were invited to participate in this cross-sectional study. Both new patients and those in follow-up were eligible. The Toronto Centre for Liver Disease is the only specialized Liver Unit in the city of Toronto and comprises a wide variety of immigrants from around the globe. We excluded patients with a history of hepatocellular carcinoma, HIV co-infection, liver decompensation and organ- or bone marrow transplant. The Research Ethics Board of University Health Network approved this study which was performed in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written consent.

Key Points

- The use of complementary and alternative medicine was common in this clinic-based population of patients with chronic hepatitis B.
- Vitamin and mineral preparations were used most frequently, whereas compounds that might damage the liver were rarely consumed.

2.2 | Data collection

To address CAM use in patients with CHB, we developed a modified version of the International Complementary and Alternative Medication Questionnaire (I-CAM-Q).¹⁶ The modified I-CAM-Q is a standardized comprehensive survey that comprises demographic, ethnic, socio-economic and clinical data, and use of 16 CAM therapies as classified by the National Center for Complementary and Alternative Medicine. The I-CAM-Q was designed for use across different populations and countries, but has not been validated. Both an English and Mandarin version of the modified I-CAM-Q was available. Patients completed the questionnaire at the time of an outpatient visit with the help of a research coordinator and if needed a translator. Any omissions or ambiguities in responses were followed up during the day of clinic visit or with telephone calls. Ethnicity-related questions involved country of birth, ethnicity, primary language, immigrant status and time since immigration. Ethnicity was categorized into five groups: Chinese (China, Hong Kong, Taiwan), South-East Asian (Philippines, Korea, Vietnam, Thailand, Cambodia, Laos, Indonesia, Malaysia), South-Asian (India, Pakistan, Afghanistan, Bangladesh, Tibet), Caucasian (Europe, Russia, Turkey, Middle-East, North-Africa, Hispanic/Latino) and Black (Africa, Haiti, Jamaica). Socio-economic information included annual household income over the last 12 months, highest level of education, employment status and private insurance coverage. Clinical data (body height and weight, duration of hepatitis B virus (HBV) infection, serum ALT, serum HBV DNA, HBeAg status, cirrhosis (defined as Metavir F4/Ishak stage 6 on liver biopsy, or radiographic evidence of cirrhosis), current and past CHB treatment, duration of CHB treatment, as well as family history of CHB and/or hepatocellular carcinoma were retrieved from patient medical records and the questionnaire.

CAM therapies have been categorized by the National Center for Complementary and Alternative Medicine of the National Institutes of Health.⁷ We obtained information on the following CAM domains and modalities from the survey: holistic therapies (homeopathy, acupuncture, naturopathy), biologically-based practices (herbal products, vitamin and mineral preparations, dietary supplements), manipulative and body-based therapies (chiropractic, massage, manipulation), mind-body medicine (meditation, spiritual therapy, visualization/guided imagery, health prayers, attendance of a traditional healing ceremony, qi gong, tai chi, yoga). For every type of CAM,

patients reported visits to CAM providers, the use of CAM products, the frequency and duration of use, the primary aim (treatment of acute or chronic symptoms of CHB, general well-being, other reason), the efficacy of CAM practice, (reasons for) non-disclosure and physician inquiry about of CAM use.

2.3 | Statistical analysis

Baseline characteristics are reported in means \pm standard deviations (SD) for continuous variables, or frequency (percentage) for categorical variables. Differences in baseline characteristics and outcomes were analysed using chi-squared test, Fisher's exact test, Student's *t* test or Mann-Whitney test, where appropriate. Current CAM use was defined as annual or more frequent use of at least one of the CAM modalities. To evaluate whether ethnicity, antiviral treatment and hepatitis activity were associated with use of CAM, predictors that were univariably associated with CAM use in logistic regression (p -value < 0.10) were analysed in multivariable logistic regression. For this analysis, the clinically most relevant CAM groups (holistic and biologically-based therapies) were included. These bio-holistic CAM therapies were selected for further analysis because of potentially relevant clinical interactions. In addition there was insufficient statistical power to include other CAM modalities. Covariates included age, sex, ethnicity, duration of CHB, current antiviral treatment, previous use of pegylated (PEG-) interferon, previous use of nucleos(t)ide analogues (NA), cirrhosis, serum ALT level, serum HBV DNA level, HBeAg status, body mass index (BMI), family history of CHB and/or liver cancer, time since immigration, immigrant status, highest level of education, employment status, annual income and private drug plan coverage. All p -values were two-sided with a significance level of 0.05. Analyses were performed in SPSS (v. 22.0, Chicago, IL).

3 | RESULTS

3.1 | Patient characteristics

A total of 600 patients were approached in the inclusion period, of whom 436 (73%) patients completed the survey. Patients were excluded due to the following: HBsAg negative ($n = 7$), relevant co-morbidity ($n = 7$), acute HBV ($n = 2$), or refusal to participate ($n = 148$). Sociodemographic and clinical characteristics of enrolled patients according to CAM use are shown in Table 1. The mean (SD) age was 49 (14) years, 263 (60%) patients were male, and 201 (46%) currently used antiviral treatment for CHB. Two hundred eight (48%) patients were Chinese, 86 (20%) South-East Asian, 28 (6.4%) South-Asian, 72 (17%) Caucasian, 39 (8.9%) Black and 3 (0.7%) patients had more than one race/ethnicity. Two-hundred and nine (48%) patients born abroad had lived for 20 or more years in Canada. Two-hundred and sixty-four (61%) patients had finished college or higher education and 235 (54%) did not have any private insurance plan. Fifteen percent was HBeAg positive, the mean ALT was 1.5 (0.3) log IU/mL, median HBV DNA 1.8 (0.0-3.6) log IU/mL, and 65 (15%) patients

were cirrhotic. Two-hundred and three (47%) patients had a family history of CHB.

Several characteristics were significantly different between CAM users and CAM non-users. Notably, CAM users were predominantly female, South-Asian or Black, had a higher socioeconomic status, and more often a family history of CHB. Other baseline characteristics were comparable between CAM users and CAM non-users.

3.2 | Patterns of CAM use

Three hundred nine (71%) patients had used CAM at least once during the past 12 months, and two hundred fifty-six (59%) patients had used CAM regularly (at least monthly; Figure 1). Biologically based (51%) and mind-body therapies (35%) were the most frequently utilized CAM domains. Within these domains, vitamin and mineral preparations (45%), spiritual practices (29%), and dietary supplements (21%) were the most common CAM modalities. The use of body-based therapies (24%) was moderate and the use of holistic practices (8.9%) was low.

CAM use was significantly different among different ethnicities (64% in Chinese, 72% in Caucasians, 76% in SE-Asians, 79% in South-Asian, and 87% in Blacks; $P = 0.03$ (Table 1 and Table S1). Specifically, mind-body medicine was practised more often by South-Asian (54%) and Black patients (77%) than other ethnic groups (22%; $P < 0.005$). Homeopathy (2.8%) and naturopathy (1.4%) were more often used by Caucasian than other groups ($P = 0.03$). The overall use of vitamin and mineral preparations (45%) and herbal product use (16%) did not differ significantly among ethnic groups. Vitamin and mineral supplements predominantly comprised of vitamin D (39%), multivitamins (38%), calcium (26%), vitamin C (19%), and omega-3 fatty acid (19%). Ginger extract (34%), milk thistle (15%) and ginseng (5.9%) were the most commonly used herbal preparations.

The use of CAM products with a reported hepatoprotective or hepatitis B infection-altering effect (milk thistle and ginger extract) was very low (3%) and was not related to subjects' liver disease severity, as was reflected by no association with serum ALT, HBV DNA or presence of cirrhosis ($P > 0.05$). The use of green tea extract (9.2%) and St. John's wort (0.2%), the only known potentially harmful CAM products in this study, was not associated with liver disease severity ($P > 0.05$).

3.3 | Attitudes towards CAM use

The main reason to use herbal products was to improve general well-being (63%; Table 2). Thirty-two percent of patients used herbal products for liver-related symptoms, compared to 2.6% of vitamin and mineral product users ($P < 0.005$). Homeopathy and spiritual therapies were rated predominantly as very helpful, whereas most other CAM therapies were considered helpful. A quarter of patients rated vitamin/mineral (24%) and other supplements (25%) as not helpful at all. The majority of patients (87%) started CAM therapy before they were diagnosed with CHB and had been using it for at

TABLE 1 Patient characteristics according to CAM use in the last year

	Overall CAM (n = 309)	No CAM (n = 127)	Bio-holistic CAM ^a (n = 235)
Demographics			
Age, y	49 (14)	48 (14)	51 (14)
Sex, male	177 (57)	86 (68)	125 (53)
Race/ethnicity			
Chinese	134 (43)	74 (58)	113 (48)
South-East Asian	65 (21)	21 (17)	48 (20)
South-Asian	22 (7.1)	6 (4.7)	11 (4.7)
Caucasian	52 (17)	20 (16)	44 (19)
Black	34 (11)	5 (3.9)	17 (7.2)
Mixed	2 (0.6)	1 (0.8)	2 (0.9)
Socio-economic factors			
Married	210 (68)	91 (72)	160 (68)
Duration of stay in Canada			
0-3 y	28 (9.1)	3 (2.4)	12 (5.1)
4-19 y	107 (35)	60 (48)	80 (34)
≥20 y	174 (56)	63 (50)	143 (61)
Residency status			
Citizen	252 (82)	20 (16)	201 (86)
Primary language			
English	187 (61)	58 (46)	137 (59)
Mandarin/Cantonese	85 (28)	51 (40)	75 (33)
Other	33 (11)	18 (14)	19 (8.2)
Education level			
≤ High school	110 (36)	62 (49)	80 (34)
College/Bachelor	161 (52)	53 (42)	122 (52)
Master/Doctorate	38 (12)	12 (9.4)	33 (14)
Employment status			
Employed	222 (72)	94 (75)	164 (70)
Unemployed	32 (10)	17 (14)	21 (8.9)
Retired	55 (18)	15 (12)	50 (21)
Annual income, Canadian dollar			
<\$25,000	69 (28)	42 (40)	49 (21)
\$25,000-\$49,999	63 (25)	32 (31)	46 (20)
\$50,000-\$99,999	77 (31)	18 (17)	60 (26)
≥\$100,000	41 (16)	13 (12)	35 (15)
Private drug plan			
None	146 (54)	89 (73)	111 (52)
50%-79%	34 (13)	7 (5.8)	29 (14)
80%-99%	49 (17)	13 (11)	38 (18)
≥100%	43 (16)	12 (10)	33 (15)
Clinical data			
Duration of HBV infection, y	17 (12)	16 (10)	18 (12)
Current CHB therapy	140 (45)	61 (48)	114 (49)
Duration, y	5.3 (9.4)	4.6 (3.1)	5.5 (10.4)

(Continues)

TABLE 1 (Continued)

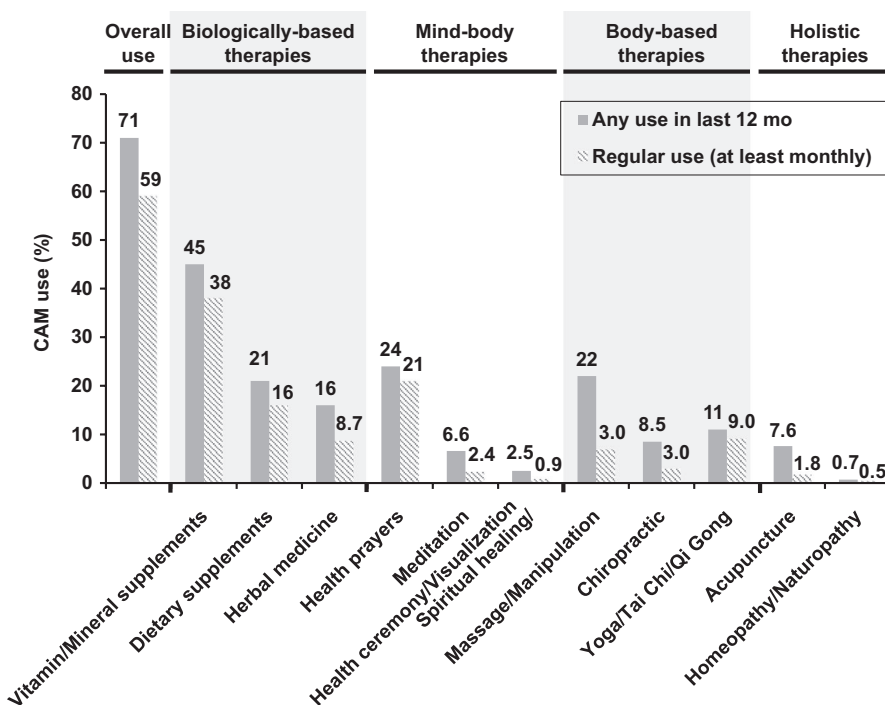
	Overall CAM (n = 309)	No CAM (n = 127)	Bio-holistic CAM ^a (n = 235)
Previous CHB therapy	135 (44)	53 (42)	107 (46)
Nucleos(t)ide analogue	128 (42)	51 (40)	100 (43)
(PEG-)interferon	24 (7.8)	10 (7.9)	19 (8.1)
Family history of CHB	156 (51)	47 (37)	126 (54)
Family history of liver cancer	52 (17)	20 (16)	45 (19)
Laboratory			
ALT, log IU/L	1.5 (0.3)	1.5 (0.2)	1.5 (0.3)
HBV DNA, log IU/mL ^b	1.9 (0.0-3.5)	1.6 (0.0-3.6)	1.6 (0.0-3.0)
HBeAg positive	43 (14)	21 (17)	26 (11)
BMI, kg/m ²	25 (4.2)	25 (4.2)	25 (4.1)
Cirrhosis	50 (16)	15 (12)	39 (17)

Data represented as n (%) or mean (standard deviation).

ALT, alanine aminotransferase; CAM, complementary and alternative medicine; CHB, chronic hepatitis B; HBV, hepatitis B virus; PEG, pegylated.

^aUse of biologically based and holistic therapies combined.

^bMedian (interquartile range).

**FIGURE 1** Use of CAM modalities in the last 12 mo in 436 patients with CHB

least 5 years, especially acupuncture (71%), visualization (57%) and herbal medicine (67%).

Forty-three percent of physicians had actively inquired about CAM use (Supplementary Table 1). Doctors had inquired about CAM use less often in Caucasian patients (33%) than in Chinese patients (46%; $P = 0.06$). Fifty-two percent of patients had not informed their physicians about CAM use, ranging from 46% (Black patients) to 64% (South-Asian patients), and this did not differ between ethnic groups. The main reasons for patients not to disclose CAM use were: not considered important to inform treating physician, non-liver

related CAM use, not inquired by physician, anticipated physician disinterest or disapproval, and already informed general practitioner or other treating physician.

3.4 | Determinants of bio-holistic CAM use

Determinants for the use of the clinically most relevant CAM group, (bio-holistic CAM, were studied with logistic regression (Table 3). The bio-holistic CAM therapies were selected because of possible clinical interactions and limited statistical power to study other

TABLE 2 Pattern of use, and attitudes towards individual CAM modalities

CAM modality	Number of users (n)	Started after CHB diagnosis (%)	Duration of use (%)		Frequency of use (%)	Reason for use (%)	Helpfulness (%)
			0-1/>1-5/>5 y	When symptomatic/daily/weekly-monthly/annually			
Biologically-based therapies							
Vitamin/mineral supplements	193	11	29/33/38	1/79/5/215	2.6/79/23	12/28/33/24	
Dietary supplements	92	3.3	11/13/76	8/45/24/24	1/5/94	9/43/12/25	
Herbal medicine	67	33	42/31/27	3/34/23/40	32/66/10	12/39/31/7	
Mind-body therapies							
Health prayer	103	21	1/7/92	1/69/34/14	11/67/28	45/43/8/2	
Meditation	28	14	18/25/57	0/29/47/25	0/6/94	50/36/11/4	
Visualization	7	43	0/43/57	0/14/29/57	0/2/98	0/50/34/17	
Spiritual healing	4	0	50/25/25	25/0/25/25	0.2/0.2/99	0/67/0/33	
Healing ceremony	3	0	0/0/100	0/33/0/67	0/1/99	0/50/0/50	
Yoga	28	14	28/21/52	0/14/62/24	0/6/94	35/38/20/7	
Tai chi	15	13	13/33/53	0/33/60/7	0/3/97	33/33/34/0	
Qi gong	12	25	18/27/55	0/33/50/17	0.2/2/98	33/33/33/0	
Body-based therapies							
Massage	95	9.5	46/25/28	3/0/32/65	0/10/90	19/38/38/5	
Chiropractic	37	16	60/19/22	8/0/35/56	0.2/3/97	22/35/41/3	
Manipulation	4	0	75/25/0	0/0/25/75	0/0/2/99	25/50/25/0	
Holistic therapies							
Acupuncture	29	12	79/14/7	3/0/28/69	0/1/99	24/45/20/10	
Homeopathy	7	13	17/50/33	17/17/17/34	0/2/98	100/0/0/0	
Naturopathy	2	0	0/50/50	0/50/50/0	0/100/0	50/0/50/0	

CAM, Complementary and alternative medicine; CHB, chronic hepatitis B.

TABLE 3 Logistic regression on bio-holistic CAM use^a

	Univariable			Multivariable		
	OR	95%CI	P	OR	95%CI	P
Demographics						
Age, y	1.03	1.02-1.05	<0.005*			ns
Sex, female vs male	2.13	1.44-3.14	<0.005*	2.18	1.35-3.59	<0.005*
Race/ethnicity						
Chinese	1.00		0.10			ns
South-East Asian	1.64	0.99-2.73				
South-Asian	0.63	0.26-1.49				
Caucasian	1.57	0.91-2.69				
Black	0.98	0.49-1.98				
Socio-economic factors						
Married	0.86	0.57-1.30	0.48			
Duration of stay in Canada						
0-3 y	1.00		<0.005*			ns
4-19 y	1.23	0.53-2.86				
≥20 y	2.55	1.13-5.77				
Residency status						
Citizen vs non-citizen	1.95	1.15-3.32	0.01*			ns
Primary language						
English	1.00		0.17			
Mandarin/Cantonese	0.75	0.49-1.14				
Other	0.53	0.28-1.02				
Education level						
≤ High school	1.00		<0.005*	1.00		<0.005*
College/Bachelor	1.89	1.24-2.86		2.03	1.23-3.34	0.01*
Master/Doctorate	2.64	1.39-5.02		2.95	1.40-6.20	<0.005*
Employment status						
Employed	1.00		<0.005*	1.00		<0.005*
Unemployed	0.88	0.47-1.65		1.45	0.72-2.96	0.30
Retired	4.14	2.35-7.29		5.22	2.72-10.03	<0.005*
Annual income, Canadian dollar						
<\$25,000	1.00		0.02*			ns
\$25,000-\$49,999	1.00	0.57-1.78				
\$50,000-\$99,999	2.09	1.19-3.65				
≥\$100,000	1.7	0.94-3.45				
Private drug plan						
None	1.00		<0.005*	1.00		0.02*
50%-79%	2.86	1.45-5.66		2.81	1.31-6.07	0.01*
80%-99%	2.08	1.18-3.67		2.07	1.09-3.94	0.03*
≥100%	1.64	0.91-2.97		1.63	0.83-3.19	0.16
Clinical data						
Duration of HBV infection						
0-9 y	1.00		0.12			
10-19 y	1.41	0.89-2.21				
20-29 yr	1.53	0.90-2.61				

(Continues)

TABLE 3 (Continued)

	Univariable			Multivariable		
	OR	95%CI	P	OR	95%CI	P
≥30 yr	2.18	1.07-4.45				
Current CHB therapy	1.13	0.77-1.65	0.53			
Previous CHB therapy	1.25	0.85-1.83	0.26			
(PEG-)interferon	1.78	0.88-3.61	0.11			
Nucleos(t)ide analogue	1.12	0.76-1.64	0.57			
Family history of CHB	1.93	1.32-2.84	<0.005*	1.65	1.07-2.55	0.03*
Family history of liver cancer	1.53	0.92-2.53	0.10			ns
Laboratory						
ALT, log IU/L	0.47	0.22-1.03	0.06			ns
HBV DNA, log IU/mL	0.89	0.82-0.97	0.01*	0.89	0.81-0.98	0.02*
HBeAg positive	0.48	0.27-0.85	0.01*			ns
BMI, kg/m ²	0.99	0.94-1.03	0.58			
Cirrhosis*	1.09	0.64-1.86	0.74			

ALT, alanine aminotransferase; CAM, complementary and alternative medicine; CHB, chronic hepatitis B; HBV, hepatitis B virus; ns, not significant; PEG, pegylated.

^aUse of biologically based and holistic therapies combined, at least monthly.

* $P < 0.05$.

CAM products. Female sex (OR for female versus male: 2.18; 95%CI: 1.35-3.59; $P < 0.005$), higher education level (Master's degree vs. High school, OR: 2.95; 1.40-6.20; $P < 0.005$), employment status (OR for retired vs employed: 5.22; 2.72-10.03; $P < 0.005$), higher private drug plan coverage (80%-100% vs. none, OR: 2.07; 1.98-3.94; $P = 0.02$), lower HBV DNA (OR: 0.89; 0.81-0.98; $P = 0.02$) and a family history of CHB (OR: 1.65; 95%CI: 1.07-2.55; $P = 0.03$) were independently associated with use of bio-holistic CAM modalities. Age, ethnicity, immigrant status, time since immigration, and primary language were not associated.

4 | DISCUSSION

In this clinic-based study, we reported the prevalence of CAM use and individual CAM modalities in a large multi-ethnic CHB cohort, and examined factors that determined CAM usage. A majority of patients used CAM in the past year (71%), ranging from 64% for Chinese to 78% in non-Asian patients. Vitamin and mineral preparations were used most frequently, followed by spiritual healing practices, body-based therapies and herbal medicine. Variables significantly associated with bio-holistic CAM use were female sex, higher socio-economic status, lower serum HBV DNA, and a family history of CHB; ethnicity and migration-related factors were not.

The use of CAM in our study was extensive compared to previous studies in CHB, but was not associated with the use of antiviral treatment or disease severity. Two previous studies in CHB reported that 46% of children used CAM, and 32% of patients in Hong Kong ever used Traditional Chinese Medicine, compared to 19% among

Chinese patients in our study.^{14,15} Other epidemiological studies in non-CHB chronic liver disease showed substantial variation in CAM use rates (27%-80%).^{8,9,11,17} The comparatively high rate of CAM use in this study could be due to the comprehensive definition of CAM, the population under study, and the setting where patients were investigated (tertiary referral centre versus family practice).^{18,19}

Prolonged and/or frequent use of presumed noxious CAM compounds can adversely impact clinical disease markers in liver disease, due to herb-drug interactions or influence of cytochrome P450 systems. These findings mainly stem from studies in liver diseases other than CHB.²⁰⁻²² In our study, patients were taking mainly 'western style' CAM products (mostly vitamins) and hardly any herbals or supplements with possible beneficial effects for HBV or liver disease. The use of potentially harmful CAM products such as green tea extract or St. John's wort was very low and not associated with liver disease severity, although this should be interpreted cautiously as few participants used these CAM products and no follow-up data was available. We are concerned when patients take a mix of herbs that are difficult to identify, but this did not occur frequently in our population, which was probably biased because all patients visited western style practitioners in a hospital. Alternatively, it might be possible that patients used CAM products which contained hepatotoxins but that they did not consider these as CAM. Nonetheless, this was the largest multi-ethnic clinic-based study in CHB and therefore probably indicative of real world CAM use in CHB in North-America. In order to monitor the (safe) use of CAM, physicians should be encouraged to actively ask about CAM use and specific harmful products, which was currently only done by less than half of the treating physicians.

This study was the first to investigate the influence of ethnicity on CAM modalities in North America, which contains a predominantly immigrant population with CHB. The demographics of Toronto, one of the most multicultural and multiracial cities worldwide where 52% of the population is composed of visible minorities, enabled us to comprehensively evaluate the role of ethnicity in CAM use.²³ CAM use in general differed by ethnicity, specifically for spiritual therapy, yoga, tai chi and homeopathy. The use of spiritual therapy was higher in South-Asian and Black patients compared to other patients. Vitamin and mineral preparation use was surprisingly similar between ethnic groups, possibly because these products have become popular among the population at large in Western countries. Earlier studies on CAM use in ethnic subgroups in Canada combined healthy subjects and patients with chronic conditions, thereby mixing different motives and patterns of use.^{17,24} Remarkably, ethnicity and migration-related factors were not associated with oral CAM use after adjustment in multivariable analysis. Other determinants, such as higher socio-economic status, were either much stronger predictors of CAM use or correlated with migration-related factors, so that any effect of ethnicity and migration-related factors might be unobservable, as seen in prior research.¹⁸ The high cost of CAM products likely restricted access to the more affluent patients, regardless of ethnic background. These findings suggest that health care providers of CHB should focus on socio-economic status rather than ethnic or cultural factors when inquiring about CAM use.

The use of CAM is widespread and growing in populations where evidence-based medicine is dominant.^{25,26} US adults spent \$33.9 billion out-of-pocket annually on CAM visits and products, whereas one in every two European citizens uses CAM, which underlines the breadth of CAM use nowadays.^{25,26} Apart from reporting CAM use rates in chronic liver disease patients, it is equally important to gain insight in why patients opt for non-conventional medical therapies. This study showed that most patients used CAM for reasons unrelated to their chronic liver disease, except for herbal medicine. A possible explanation is that the most commonly used herbal products milk thistle (*Silybum marianum*) and several Traditional Chinese Medicine products have been associated with hepatoprotective effects, while the efficacy of other CAM therapies is less clear.^{12,27-30} Additionally, the non-liver related use of CAM could reflect an increasing demand for 'salutogenesis', an approach that focuses on determinants of well-being, rather than on determinants of disease, and is key to the CAM paradigm.³¹

Strong aspects of this study are the inclusion of a large, multi-ethnic cohort of CHB patients who completed an extensive survey on CAM-related factors. Conversely, the inherent recall bias for questionnaires and cross-sectional design restricted us to study long-term consequences of CAM use. Future studies on CAM use in CHB could focus on these long-term effects and associated factors.

In summary, CAM use in this clinic-based population of CHB patients was common and the CAM products that patients used, primarily vitamin and mineral preparations, appeared to be safe. Few patients had used CAM products that were considered to be harmful. CAM use was associated with female sex, higher socio-economic

status, lower HBV DNA and a family history of CHB; not with ethnic background, antiviral treatment or liver disease severity. Most treating physicians had not inquired about the use of CAM, neither had most of the patients discussed its use.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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