

The effects of *Curcuma xanthorrhiza* rhizome simplicia and *Camellia sinensis* green tea in a patient with chronic hepatitis B infection: a case report

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<https://doi.org/10.22146/ijpther.4567>

ABSTRACT

Submitted: 18-05-2022
Accepted : 12-10-2022

Keywords:

C. xanthorrhiza rhizome;
C. sinensis green tea;
chronic hepatitis B;
interferon;
antiviral

The hepatitis B virus (HBV) causes acute and chronic liver infections which can be treated by using interferon and antiviral. However, the treatment is relatively expensive. We reported here a case of a patient with chronic hepatitis B who had negative seroconversion without interferon (IFN) and antiviral treatment after herbal consumption. A retrospective investigation showed that the patient consumed *Curcuma xanthorrhiza* rhizome and *Camellia sinensis* green tea. These herbs were widely both *in vitro* and *in vivo* studied for their effects against HBV infection, although the clinical studies are limited. This case reported the effect of *C. xanthorrhiza* rhizome and *C. sinensis* green tea consumption in a patient with chronic hepatitis B. A female patient with chronic hepatitis B infection at the age of 32 y.o. had been taking neuro vitamins regularly for a year before infection detected. She was an asymptomatic patient with normal limits liver function, positive HBsAg and negative anti-Hbs. At the age of 45, she started taking *C. xanthorrhiza* rhizome simplicia equivalent to 5mg of curcumin twice daily and drinking *C. sinensis* green tea regularly. Six years later, HBsAg was not detected and her liver function remained within normal limits and Anti-HBs were detected 5 years later. In conclusion, the consumption of *C. xanthorrhiza* rhizome and *C. sinensis* green tea can against chronic hepatitis B infection by eliminate HBV dan induce anti-HBs.

ABSTRACT

Virus hepatitis B (HBV) dapat menyebabkan infeksi hepar akut dan kronis yang dapat diobati dengan interferon dan antivirus. Namun demikian, pengobatan ini cukup mahal. Dilaporkan kasus seorang pasien yang menderita hepatitis B kronis yang menunjukkan serokonversi negative tanpa pengobatan interferon dan antiviral setelah mengkonsumsi herbal. Dari penelusuran secara retrospektif, diketahui pasien tersebut mengkonsumsi rimpang (temulawak) *Curcuma xanthorrhiza* dan daun teh hijau (*Camellia sinensis*). Kedua herbal tersebut telah banyak diteliti baik secara *in vitro* dan *in vivo* efeknya melawan infeksi HBV, namun penelitian klinik pada manusia masih terbatas. Pada kasus ini dilaporkan efek konsumsi rimpang *C. xanthorrhiza* dan teh hijau *C. sinensis* pada pasien hepatitis B kronis. Seorang pasien hepatitis B kronis yang terinfeksi saat berusia 32 tahun, sejak setahun sebelumnya telah mengkonsumsi neurovitamin secara teratur. Pasien tidak bergejala dengan fungsi hepar dalam batas normal, pemeriksaan HBsAg positif dan anti-HBs negatif. Pada usia 45 tahun, pasien diterapi dengan simplisia rimpang *C. xanthorrhiza* setara dengan 5mg kurkumin dua kali sehari dan teh hijau *C. sinensis* secara teratur. Enam tahun kemudian, HBsAg tidak terdeteksi, fungsi hepar tetap dalam batas normal dan anti HBs terdeteksi lima tahun setelah hilangnya HBsAg. Dapat disimpulkan, mengkonsumsi rimpang *C. xanthorrhiza* dan teh hijau *C. sinensis* dapat melawan infeksi hepatitis dengan mengeliminasi HBV dan menginduksi anti-HBs.

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INTRODUCTION

Hepatitis B virus (HBV) is a non-cytopathic hepatotropic DNA virus belonging to the *Hepadnaviridae* family that causes acute and chronic liver infection. It is estimated that HBV infected more than 300 million people in Asia and Africa.¹ Acute liver infection can lead to serious illnesses in which approximately 0.5% of the cases resulting in fatal hepatitis. Chronic liver infection can also cause several diseases, such as liver fibrosis and liver cirrhosis in which almost 25% of cases lead to untreatable hepatocellular carcinoma (HCC).^{2,3}

Treatment of chronic HBV infection generally involves interferon- α (IFN α) or antiviral such as lamivudine, adefovir, and entecavir. Interferon- α has direct immunostimulatory and antiviral properties, however it is only effective in one-third of patients and has serious side effects. The antivirals suppress the virus by directly interfering with the synthesis of HBV genomic DNA, which may result in viral resistance to these drugs.² To avoid these negative effects, there is a need for alternative treatments. Some herbs have been used traditionally to treat infection including HBV infection such as *Curcuma xanthorrhiza* rhizome and *Camellia sinensis* green tea.

Curcuma xanthorrhiza, well known as Java Turmeric worldwide with local name temulawak, is a member of the *Zingiberaceae* family. It is native to Indonesia that traditionally used as ingredients of jamu, a traditional medicine from Indonesia. *Curcuma xanthorrhiza* is an herbal tonic to maintain health. It has been used to protect liver, to treat some diseases such as diabetes, rheumatism, cancer, hypertension and heart disease. *Curcuma xanthorrhiza* has been proven to have anti-inflammatory, antioxidant, antihypertensive, antihepatotoxic, antibacterial, and antifungal effects.³⁻⁵ Curcumin and xanthorrhizol are the main active constituents isolated from *C. xanthorrhiza*.⁴

Green tea is made from the unfermented leaves of *C. sinensis*,

Theaceae family. It contains rich polyphenols such as epigallocatechin-3-gallate as main constituent, catechins, epicatechin, epigallocatechin, and epicatechin gallate. Epigallocatechin-3-gallate was proven can protect cells damages by inhibiting DNA damage and oxidation of low-density lipoproteins. It has also several biological activities such as antioxidant and anti-inflammatory.⁶ In human society, tea is consumed as a daily health drink in addition to coffee, particularly in the Chinese and Japanese communities. Drinking tea has become a daily habit where tea is consumed similarly to water. It is also used as a carrier for taking medicine in tablets and capsule forms.

In vitro and *in vivo* studies have proven that both *C. xanthorrhiza* and *C. sinensis* green tea have antioxidant and hepatoprotective activities.^{5,6} However, clinical studies of *C. xanthorrhiza* and *C. sinensis* green tea in patients with chronic hepatitis B infection are limited. In this article we reported the effect of *C. xanthorrhiza* rhizome and *C. sinensis* green tea consumption in a patient with chronic hepatitis B by evaluating HBsAg and anti-HBs levels, and hepatoprotective activity.

CASEA 67 y.o. female outpatient of Dr. AW Sjahranie Distric Hospital, Samarinda with 56 kg body weight has had history of some diseases as follows allergic rhinitis since adolescence, Bell's Palsy at the age of 31 years, hepatitis B infection detected at the age of 32 years, fungus on the toenails, and a 10 mm diameter wart on the abdomen skin since the age of 40 years, and mild hypertension since the age of 52 years. She has never been seriously symptoms that led to hospitalization. Her physical condition was good. Since the age of 30 years, she has performed one-hour exercise twice a week, then from the age of 50 years, the frequency has been increased to 15 min daily. She does not like to eat vegetables, but she eats fruits like papaya or bananas every day, sometimes oranges and apples as well. She lived with a regular routine

and worked at her workplace until retirement.

In 1987, a patient aged 32 y.o. was randomly detected as positive HBsAg without symptoms from a laboratory examination at AW Sjahranie Distric Hospital, Samarinda (FIGURE 1 and TABLE 1). A year before, she experienced

Bell's Palsy and treated with acupuncture and oral administration of neuro vitamins (B1 100mg, B6 200mg, and B12 200µg) twice daily. During the next 13 years, the HBV infection was never treated with antivirals or IFN-α and she only took the neuro vitamin tablets regularly.

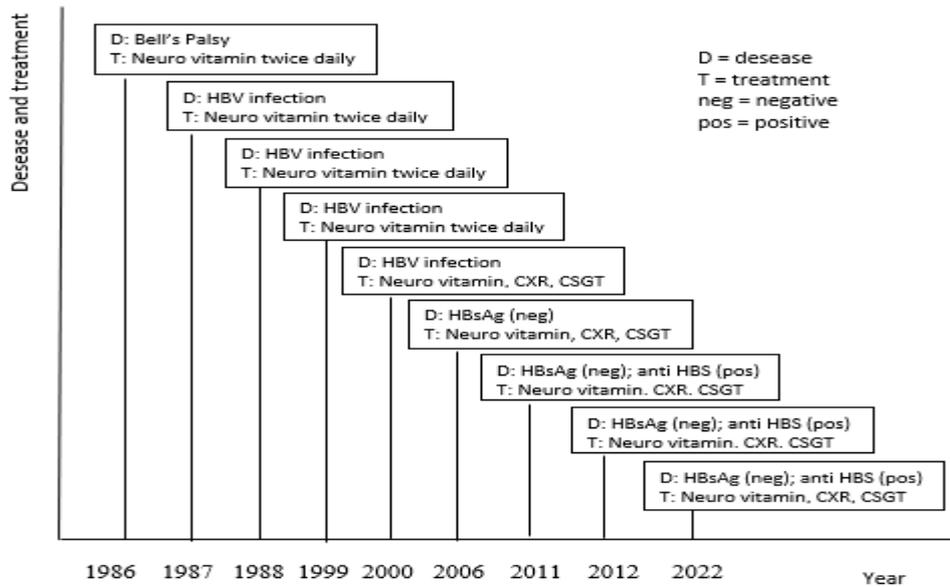


FIGURE 1. The course of patient with hepatitis B infection and the treatment

TABLE 1. Laboratory examination results of the patient from 1986 to 2022.

Date	Laboratory examination results				
	SGOT (U/L)	SGPT (U/L)	Alkaline phosphatase (U/L)	HBSAg (mIU/mL)	Anti-HBS (mIU/mL)
Oct 16, 1986	6	10	10		
Dec 07, 1987	7	9		+	-
Mar 24, 1988	12	17		+	-
July 29, 1999				277.81	-
Feb 17, 2000	83	49	78	267.45	-
Nov 08, 2002	20.9	18.7	0.94		
June 16, 2006	23	13		3.09	-
July 20, 2006	21.6	15.7		- 1.41	-
Sept 21, 2011	46	46		-	207
Oct 13, 2012	25	24		-	157
Jan 04, 2022	25	24		-	124.6

The normal limit for SGPT is 9-36 u/L, SGOT is 10-31 u/L, and ALP is 74-311 u/L; This data was taken from the results of laboratory examinations at AW Sjahranie District Hospital, Samarinda.

In 2000, since the age of 45 she has been treated with 500mg *C. xanthorrhiza* rhizome capsules, which is equivalent to 5mg of curcumin (produced by PT JI Surabaya), twice daily in combination with a *C. sinensis* green tea. The tea was prepared by pouring 1500mL of boiling water that had been allowed to stand until a temperature of about 80 °C into a teapot containing 10g of dried *C. sinensis* green tea leaves (purchased from M Swalayan Samarinda). The *C. sinensis* green tea solution was taken as a substitute for water at least three 200 mL cups daily, either warm or cold. The *C. sinensis* green tea leaf residue can be refilled once, as in the above procedure. The initial goal of consuming *C. xanthorrhiza* rhizome and *C. sinensis* green tea was to protect the liver from the effects of HBV infection, such as oxidative stress or liver cell injury.

In 2006, after six years later, HBsAg test was conducted with negative result. In 2011, after five years later, HBs antibody test was also conducted with positive result with a titer of 207 mIU/mL (TABLE 1). In 2012, after one year later, the anti-HBs titer was 157 mIU/mL. In 2022, after ten years later a repeat test was performed to confirm whether she had recovered from the chronic hepatitis B infection. The HBsAg result was negative, and the anti-HBs titer was 124.6 mIU/mL.

Before treatment with both herbs, the patient had a history of diseases such as allergic rhinitis and fungal infection on her toenails. Since drinking *C. xanthorrhiza* rhizome with *C. sinensis* green tea, other effects such as surface wounds due to falls or knife cuts healed quickly without any administration of anti-inflammatory drugs, fungal infections of the toenails improved, and the patient's previous allergic rhinitis did not recur. Furthermore, no side-effects to be observed after the administration of *C. xanthorrhiza* rhizome or *C. sinensis* green tea for 21 years.

DISCUSSION

An increase in oxidative stress and a significant reduction in vitamins such as carotene, B, C, D, and E in the serum of patients with HBV infection was reported.⁷⁻⁹ The disturbs of cellular redox balance cause severe oxidative stress leading to more active viral replication.⁸ Wallace *et al.*¹⁰ reported that 100 mg/day of thiamin (vitamin B1) reduced aminotransferase to normal levels and brought HBV DNA to undetectable levels in patients with hepatitis. Another study in HCC patients also showed that plasma glutathione, a biomarker to evaluate oxidative status, and vitamin B2 and B6 levels were lower, therefore requiring vitamin B supplementation.¹¹

In this case, patient was diagnosed chronically HBV infection with remained positive HBsAg for more than 13 years before being treated with *C. xanthorrhiza* rhizome with *C. sinensis* green tea. During HBV infection, the patient was asymptomatic, with liver function parameters such as serum glutamic pyruvic transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT), and alkaline phosphatase (ALP) levels within normal limits. Administration of neuro vitamin-containing vitamins B1, B6, and B12 continuously for a year before HBV infection is thought to help maintain the SGOT and SGPT at normal levels. Previous neuro vitamin supplementation may have rapidly restored the cellular redox balance when infected with HBV, resulting in mild oxidative stress resulting in no HBV replication for 13 years despite the positive HBsAg tests, and normal liver function (FIGURE 1 and TABLE 1).As oxidative stress is a pathogenesis mechanism that contributes to the initiation and progression of liver damage in inflammatory liver disorders, including acute and chronic hepatitis, antioxidant therapy is an appropriate strategy for treating acute and chronic

hepatitis.⁹ Many natural compounds can reduce reactive oxygen species (ROS) that lead to directly reduce and protect oxidative stress by activating the endogenous defense systems. Flavonoids are efficient ROS suppressors due to their radical scavenging properties and are inducers of cellular antioxidant systems. In addition, lecithin, vitamin B complex, and tocopherol acetate have been reported can reduce oxidative stress by controlling ethanol-induced immunomodulatory activity and supporting antioxidant systems.⁸

Initially, the administration of *C. xanthorrhiza* rhizome with *C. sinensis* green tea aimed to protect the liver from oxidative stress and liver cell injury due to the HBV infection. The protection was achieved as shown with the normal liver function or the normal SGOT and SGPT levels. It is postulated that curcumin in *C. xanthorrhiza* rhizome and epigallocatechin-3-gallate in *C. sinensis* green tea play role in the protection of liver from the HBV infection effects and the suppression of HBsAg expression. Curcumin, active constituent of *C. xanthorrhiza* rhizome, has several biological activities, including anti-inflammatory, anticancer, antioxidant, and wound-healing effects. *In vitro* and *in vivo* studies reported that curcumin has activity to prevent and against oxidative stress in the liver by repairing antioxidant enzymes, including glutathione S-transferase (GST), glutathione reductase (GR), glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT), as well as inhibiting ROS production.^{8,9} HBV infection can cause hepatitis, liver cirrhosis, and HCC. The HBV genome was made partly from double-stranded relaxed circular DNA (rcDNA), with a size of 3020–3320 bp. After the virus infects hepatocytes, rcDNA is released into the nucleus and converted into covalently closed circular DNA (cccDNA), which, together with histone bonds, constitutes the minichromosome. In addition, cccDNA serves as a template for viral replication and mRNA synthesis. It is the

source of persistent and recurrent HBV infection. Nucleotide analog antivirals can efficiently inhibit HBV replication. However, they do not clean up residual cccDNA.¹² Curcumin not only inhibits intracellular HBV replication, HBsAg and HBeAg expressions but also exhibits a potent inhibitory effect on HBV cccDNA. It also reduces chromosomal and histone H3/H4-bound cccDNA levels.¹²

Hepatitis B virus is a double-stranded DNA virus with a small genome that highly contagious and can not be cured completely. Although IFN- α and nucleotide analog antivirals have played a major role in HBV infection therapy, they can not be for a long duration due to their side effects such as myopathy, neuropathy, pancreatitis, renal impairment, and the development of resistance.¹³ Therefore, alternative therapy of HBV infection is urgently needed. *Camellia sinensis* could be alternative therapy against HBV infection.

Green tea is prepared from unfermented *C. sinensis* leaves, which are rich in catechin polyphenols. More than 40% of the total catechins in green tea are epigallocatechin-3-gallate which has antiviral activity on both DNA and RNA viruses. The extracts of *C. sinensis* and epigallocatechin-3-gallate can inhibit ROS production and have anti-HBV activity.¹ Epigallocatechin-3-gallate can also suppress HBV replication and expression by inhibiting HBV promoter transcription and DNA replication, inducing incomplete viral autophagy, and inhibiting chronic pathogenesis.¹³ Green tea also has antioxidant and hepatoprotective activities,^{14,15} such that it can reverse oxidative stress that may occur due to HBV infection. By capturing free radicals, the balance between redox and cellular antioxidants is maintained, which results in no liver cell damage. Preparing the CSGT solution using 80°C water helps obtain optimal secondary metabolites (catechins and tannins) and lowers the caffeine content.¹⁶ The catechins and tannins in CSGT exhibit antioxidant activity.

In this study, the decrease in

HBsAg titer until not detected was observed after the administration of *C. xanthorrhiza* rhizome capsules and drinking *C. sinensis* green tea for six years. This indicates that curcumin in *C. xanthorrhiza* rhizome inhibits intracellular HBV replication, HBsAg, and HBeAg expression. It also demonstrated a potent inhibitory effect on HBV cccDNA. In addition, epigallocatechin-3-gallate in green tea suppressed HBV replication and expression. Further study is needed to investigate the mechanism of combination effects between *C. xanthorrhiza* rhizome and *C. sinensis* green tea in suppression of HBV replication.

In patients with chronic hepatitis B, the response of the host's T and B cells to the HBV antigens is exhausted resulting in uncontrolled and persistent HBV replication and leading to the development of diseases such as cirrhosis and HCC.^{17,18} Treatment with IFN- α and nucleotide analogue antivirals suppresses HBV replication and slows disease progression. The end goal of chronic HBV treatment is the sustained loss of HBsAg with or without seroconversion to HBs antibodies as they show immunity to HBV and a better prognosis.¹⁷ The occurrence of HBsAg seroclearance in patients with chronic HBV infection is very low, only 0.4-2% per year in Caucasian patients and 0.1-0.8% per year in Chinese patients. Even in patients with chronic hepatitis B treating with IFN- α , the HBsAg seroclearance only increased by 6%.¹⁸

HBsAg seroclearance after six years of the administration of *C. xanthorrhiza* rhizome capsules and drinking *C. sinensis* green tea and another five years until anti-HBs appeared indicated that the patient underwent a seroconversion induced by these herbs and neuro vitamins consumption. The patient has a good physical condition as showed never had serious ill, adequate sleep for six hours without interruption, and regular exercise even though in shorter duration. These conditions contribute to increase

immune system of the patient during her chronic HBV infection, such that her T cells response to viral antigens were stronger and more sustained, resulting in controlled HBV replication.^{19,20} When HBV levels decrease in such cases, it is postulated that an immune response induces B cells to produce HBV antibodies. This situation can occur as oxidative stress does not increase, and liver cells are well protected by the administration of *C. xanthorrhiza* rhizome capsules and drinking *C. sinensis* green tea and neuro vitamins. The patient did not experience spontaneous remission as her HBsAg remained positive in the 13 years period before the administration of administration of *C. xanthorrhiza* rhizome capsules and drinking *C. sinensis* green tea. Therefore, these herbs have the potential to become alternative medicine in chronic hepatitis B treatment. However, further research with more patients is needed.

As shown in TABLE 1, the HBV was not detected in the patient after six years of consuming *C. xanthorrhiza* rhizome capsules and drinking *C. sinensis* green tea. It may due to the doses of these herbs were too small. The dose of *C. xanthorrhiza* rhizome and *C. sinensis* green tea were not increased based on the consideration of avoiding side effects. Anti-HBs in the patient appeared after five years of negative HBsAg results. This period could be shorter, as the anti-HBs were tested until the fifth year. Ten years later, anti-HBV was still detected, showing that the patient has completely recovered from the chronic HBV infection.

During the administration of *C. xanthorrhiza* rhizome capsules and drinking *C. sinensis* green tea, other beneficial effects occurred, namely, wounds on the skin due to knife cuts or falls healed without the administration of anti-inflammatory drugs, fungal growth in toenails was inhibited, and allergic rhinitis disappeared. This is in accordance with studies showing that curcumin has an anti-inflammatory

effect,²¹ inhibits the growth of fungi,²² and has an anti-allergic rhinitis effect.²³ More importantly, no toxic effects were observed during the consumptions of these herbs. In addition to small doses of *C. xanthorrhiza* rhizome and *C. sinensis* green tea, the herbs administered to the patient were dried simplicia of *C. xanthorrhiza* rhizome and brewed *C. sinensis* green tea, which still contain various secondary metabolites that may reduce the toxicity of curcumin and epigallocatechin-3-gallate.

A limitation of this study is that the laboratory examinations were not performed regularly, particularly when HBsAg becomes negative until anti-HBs appear. Therefore, the precise time the body's immune response inducing HBs antibodies production is unknown and could only be estimated after five years.

CONCLUSION

In conclusion, the administration of *C. xanthorrhiza* rhizome capsules and drinking *C. sinensis* green tea help eliminate HBV, induce anti-HBs, and cure the patient from chronic HBV infection.

ACKNOWLEDGEMENTS

Authors would like to thank the patient for her collaborations.

REFERENCES

1. Thanigaivel S, Durgadevi H, Rohan N, Mythily V, Elanchezhiyan M. Antihepatitis B virus (HBV) activity of extracts of *Camellia sinensis*, the green tea. *World Res J Med Aromat Plant* 2013; 2(1):039-043.
2. Karamese M, Aydogdu S, Karamese SA, Altoparlak U, Gundogdu C. Preventive effects of a major component of green tea, epigallocatechin-3-gallate, on hepatitis-B virus DNA replication. *Asian Pac J Cancer Prev* 2015; 16:4199-202.
3. Ilene ASP, Sandhika W, Hasanatuludhhiyah N. Effect of Javanese turmeric (*Curcuma xanthorrhiza*) extract on hepatitis model of alcohol-induced mice. *JKB* 2020; 31(1):39-42.
4. Salleh NAM, Ismail S, Halim MRA. Effects of *Curcuma xanthorrhiza* extracts and their constituents on phase II drug-metabolizing enzymes activity. *Pharmacognosy Res* 2016; 8(4):309-15. <https://doi.org/10.4103/0974-8490.188873>
5. Buonomo AR, Scotto R, Nappa S, Arcopinto M, Salzano A, Marra AM, et al. The role of curcumin in liver diseases. *Arch Med Sci* 2019; 15(6):1608–20. <https://doi.org/10.5114/aoms.2018.73596>
6. Oliveira RMM. Quantification of catechins and caffeine from green tea (*Camellia sinensis*) infusions, extract, and ready-to-drink beverages. *Ciênc Tecnol Aliment Campinas* 2012; 32(1):163-6.
7. Lin CC, Liu WH, Wang ZH, Yin MC. Vitamins B status and antioxidative defense in patients with chronic hepatitis B or hepatitis C virus infection. *Eur J Nutr* 2011; 50:499-506.
8. Esrefoglu M. Oxidative stress and benefits of antioxidant agents in acute and chronic hepatitis. *Hepat Mon* 2012; 12(3):160-7. <https://doi.org/10.5812/hepatmon.837>
9. Farzaei MH, Zobeiri M, Parvizi F, El-Senduny FF, Marmouzi I, Coy-Barrera E, et al. Curcumin in liver diseases: a systematic review of the cellular mechanisms of oxidative stress and clinical perspective. *Nutrients* 2018; 10:855. <https://doi.org/10.3390/nu10070855>
10. Wallace, Elizabeth A, Weeks WB. Thiamine treatment of chronic hepatitis B infection. *Am J Gastroenterol* 2001; 96:864-8.
11. Lin CC, Yin MC. B vitamins deficiency and decreased anti-oxidative state in patients with liver cancer. *Eur J Nutr*

- 2007; 46(5):293–9.
12. Wei ZQ, Zhang YZ, Ke CZ, Chen HX, Pan R, He YL, *et al.* Curcumin inhibits hepatitis B virus infection by downregulating cccDNA-bound histone acetylation. *World J Gastroenterol* 2017; 23(34):6252-60.
 13. Wang YQ, Li QS, Zheng XQ, Lu JL, Liang YR. Review: Antiviral effects of green tea EGCG and its potential application against COVID-19. *Molecules* 2021; 26:3962. <https://doi.org/10.3390/molecules26133962>
 14. Reddy MA, Kumar BK, Boobalan G, Reddy MK, Kumar CSVS, Reddy AG, *et al.* Hepatoprotective potential of green tea extract against experimental hepatotoxicity in rats. *Indian J Pharm Sci* 2017; 79(1):58-64.
 15. Cao SY, Li BY, Gan RY, Mao QQ, Wang YF, Shang A, *et al.* The *in vivo* antioxidant and hepatoprotective actions of selected Chinese teas. *Foods* 2020; 9:262. <https://doi.org/10.3390/foods9030262>
 16. Saklar S, Ertas E, Ozdemir IS, Karadeniz B. Effects of different brewing conditions on catechin content and sensory acceptance in Turkish green tea infusions. *J Food Sci Technol* 2015; 52(10):6639-46.
 17. Tout I, Loureiro D, Mansouri A, Soumelis V, Boyer N, Asselah T. Hepatitis B surface antigen seroclearance: immune mechanisms, clinical impact, importance for drug development. *J Hepatol* 2020; 73:409-22. <https://doi.org/10.1016/j.jhep.2020.04.013>
 18. Lau GKK, Suri D, Liang R, Rigopoulou EI, Thomas MG, Mullerova I, *et al.* Resolution of chronic hepatitis B and anti-HBs seroconversion in humans by adoptive transfer of immunity to hepatitis B core antigen. *Gastroenterol* 2002; 122:614-24. <https://10.1053/gast.2002.31887>
 19. Besedovsky L, Lange XT, Haack M. The sleep-immune crosstalk in health and disease. *Physiol Rev* 2019; 99:1325-80. <https://doi.org/10.1152/physrev.00010.2018>
 20. Peake JM, Neubauer O, Walsh NP, Simpson RJ. Recovery of the immune system after exercise. *J Appl Physiol* 2017; 122:1077-87. <https://doi.org/10.1152/jappphysiol.00622.2016>
 21. Fu YS, Chen TH, Weng L, Huang L, Lai D, Weng CF. Pharmacological properties and underlying mechanisms of curcumin and prospects in medicinal potential. *Biomed Pharmacother* 2021; 141:111888. <https://doi.org/10.1016/j.biopha.2021.111888>
 22. Praditya D, Kirchhoff L, Brüning J, Rachmawati H, Steinmann J, Steinmann E. Anti-infective properties of the golden spice curcumin. *Front Microbiol* 2019; 10:912. <https://doi.org/10.3389/fmicb.2019.00912>
 23. Wu S, Xiao D. Effect of curcumin on nasal symptoms and airflow in patients with perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2016; 117:697-702. <https://doi.org/10.1016/j.anai.2016.09.427>