



EVALUATING THE IMPACT AND HEMATOLOGICAL ASSESSMENT OF TENOFOVIR WITH *MELISSA OFFICINALIS* EXTRACT IN DECOMPENSATED CHRONIC LIVER DISEASE PATIENTS WITH HEPATITIS: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Chronic hepatitis B (CHB) and decompensated chronic liver disease (DCLD) pose substantial global health challenges, often leading to severe liver dysfunction and potentially life-threatening complications. Hepatic decompensation, characterized by the liver's inability to perform its essential functions, is a critical consequence of CHB and DCLD, underscoring the need for effective management strategies.

Objectives: To determine the effectiveness of antiviral drug tenofovir with *Melissa officinalis* in preventing hepatic decompensation in patients with chronic hepatitis B and decompensated cirrhosis.

Duration and Place of Study: The study was conducted between August 2023 and July 2024 at the Department of Gastroenterology in Dow University of Health Sciences.

Methodology: A comprehensive study involving 191 patients with chronic hepatitis B and decompensated cirrhosis compared the efficacy of two antiviral therapies, Tenofovir and *Melissa officinalis* leaves extract in preventing hepatic decompensation episodes. These episodes include severe complications such as ascites, variceal bleeding, hepatic encephalopathy and spontaneous bacterial peritonitis. The study collected detailed demographic, clinical and laboratory data to assess liver function and disease severity. By evaluating the effectiveness of these treatments, the study aimed to inform optimal management strategies for patients with chronic hepatitis B and decompensated cirrhosis, ultimately improving clinical decision-making and patient outcomes.

Results: The study found that antiviral treatment was effective in preventing hepatic decompensation in 60.2% of patients. Tenofovir demonstrated superior efficacy (76.4%) as compared to *Melissa*

officinalis (53.7%) ($p=0.004$). Significant predictors of efficacy included INR levels ($\text{Exp(B)}=0.208$, $p=0.014$) and the type of treatment (Tenofovir vs *Melissa officinalis*) ($\text{Exp(B)}=2.432$, $p=0.022$).
Conclusion: Antiviral therapy, Tenofovir in particular, can effectively reduce hepatic decompensation in cirrhotic and HBV-related chronic hepatitis B infection patients. INR is a key predictive indicator for successful therapy.

Keywords: Chronic hepatitis B, cirrhosis, Hepatic decompensation, Antiviral therapy, Tenofovir, *Melissa officinalis*

INTRODUCTION

Chronic hepatitis with decompensated chronic liver disease (DCLD) is a serious condition characterized by significant liver dysfunction, often resulting from long-standing hepatitis B or C virus infection and cirrhosis[1,2]. Patients with decompensated chronic liver disease (DCLD) experience severe symptoms, including hepatic failure, variceal hemorrhage, hepatic encephalopathy and jaundice which significantly impact their quality of life. Traditional management strategies focus on controlling symptoms and complications, such as using diuretics for ascites and lactulose for hepatic encephalopathy and in severe cases, liver transplantation may be considered. However, these approaches do not address the underlying viral infection and ongoing liver damage. The development of antiviral therapies has revolutionized the treatment of chronic hepatitis, particularly for decompensated chronic liver disease (DCLD) patients. Antiviral drugs, such as tenofovir for hepatitis B and direct-acting antivirals for hepatitis C, effectively inhibit viral replication, reduce liver inflammation and slow disease progression[3-5]. By targeting the virus and reducing immune-related liver damage, antiviral therapy can stabilize liver function and improve patient outcomes, offering new hope for managing this high-risk patient population.

Antiviral therapy plays a crucial role in managing decompensated chronic liver disease (DCLD) and chronic hepatitis by preventing hepatic decompensation and improving patient prognosis[6]. By suppressing viral activity, these therapies allow the liver to regain functional capabilities, reducing complications such as variceal hemorrhage, hepatic encephalopathy and ascites. Early initiation of antiviral therapy can preserve liver function and delay disease progression[7]. Although restoration of liver function may not always be possible in advanced stages, antiviral therapies can stabilize patients, enhance survival and improve quality of life. Effective antiviral treatments like Tenofovir can significantly impact patient outcomes, and determining their real-life efficacy is essential for maximizing management protocols and improving prognosis[8-9].

In addition to antiviral therapy, certain natural compounds like *Melissa officinalis* have shown promise in exhibiting antiviral and antioxidant properties, which could contribute to their potential health benefits. However, further research is needed to fully understand the benefits and limitations of these compounds[10]. *Melissa officinalis*, a member of the Lamiaceae family, is a traditional herbal medicine with a rich history of use in Mediterranean countries and widespread growth across North America, Europe, and Asia. This plant has been utilized for various medicinal purposes, leveraging its extracts and essential oil for their pharmacological properties[11,12]. The leaves extract of *Melissa officinalis* have demonstrated a range of beneficial effects, including antimicrobial, anticancer, antiviral, antioxidant, and anti-inflammatory activities. Studies suggest that its antiviral effects may be attributed to its phenolic compounds, such as rosmarinic acid and caffeic acid, which can interfere with viral replication and entry into host cells. *Melissa officinalis* extracts have been shown to exhibit antiviral activity against various viruses, including herpes simplex virus (HSV) and influenza virus[13]. The antiviral mechanism may involve inhibition of viral attachment, penetration or replication, as well as modulation of the host's immune response. Further research is needed to elucidate the specific molecular mechanisms underlying the antiviral effects of *Melissa officinalis* and to explore its potential therapeutic applications.

Overall, antiviral therapy is a crucial component in the management of decompensated chronic liver disease and chronic hepatitis, and early initiation of treatment can significantly impact patient outcomes.

METHODOLOGY

This study was conducted at DUHS between August 2023 to July 2024, enrolling 191 patients with chronic hepatitis B (CHB) and decompensated chronic liver disease (DCLD). The patients were selected using a non-probability consecutive sampling technique, based on a 95% confidence level, 7% margin of error and an expected efficacy of 58% for antiviral treatments in preventing hepatic decompensation episodes. The study included patients of both genders, aged 18 years or older with a confirmed diagnosis of CHB and decompensated cirrhosis. Patients with co-infections such as hepatitis C, hepatitis D, or HIV, as well as those with prior solid organ transplantation were excluded. Baseline demographic data, including age, sex, liver function tests, HBV-DNA levels, CPT and MELD scores were recorded for each patient. The study aimed to evaluate the effectiveness of antiviral treatments in preventing episodes of hepatic decompensation in this patient population.

The patients received Tenofovir with extract of *Melissa officinalis* leaves extracts. The efficacy of treatment was evaluated over 1 year period, focusing on preventing further episodes of hepatic decompensation and achieving overall clinical improvement. Treatment success was defined by the absence of new decompensation episodes, virological response, biochemical response, liver function improvement, and survival without liver transplantation.

Patients who experienced worsening decompensation, required liver transplantation, or died due to liver-related complications were considered treatment failures

Ethical considerations

The study was approved by the institutional IRB of Dow University of Health Sciences.

Data management and statistical analysis

The study used SPSS 22.0 for statistical analysis. Continuous data were summarized based on their distribution, with normally distributed data presented as mean $\pm$ standard deviation and non normally distributed data as median with interquartile range. Categorical data were presented as frequencies and percentages. Kaplan-Meier survival analysis was used to estimate cumulative survival rates and a p-value <0.05 was considered statistically significant. To evaluate changes over time was assessed using multivariable logistic regression models, which reported odds ratios with 95% confidence intervals.

RESULTS

The study's patient demographics and baseline characteristics revealed a mean age of 53.34 years, with a notable male predominance, comprising 85.3% of the study population, while females accounted for 14.7%. The laboratory parameters indicated active HBV infection, with a mean HBV DNA level of 5.23 log₁₀ IU/mL and significantly elevated alanine aminotransferase (ALT) levels, averaging 311.56 U/L.

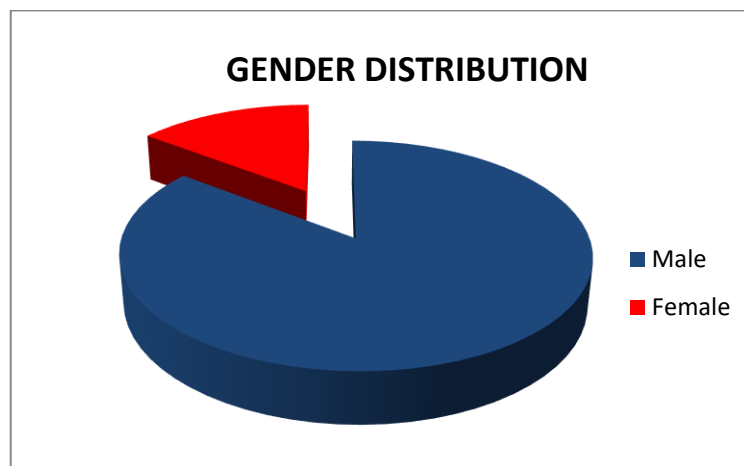


Figure 1 showed the Gender distribution of the patients

Other key laboratory values included total bilirubin, albumin, international normalized ratio (INR), platelet count, and creatinine, which provided insight into the patients' liver function and overall health status.

The mean duration of disease was 1 year, indicating a relatively long-standing condition. In terms of treatment history, 52.4% of patients had previously received nucleos(t)ide analogues treatment, while 47.6% were treatment-naïve.

The current treatment distribution showed that 71.2% of patients were receiving Tenofovir, while 28.8% were receiving *Melissa officinalis*. These baseline characteristics provide a comprehensive understanding of the patient population and their disease profiles, allowing for a more nuanced evaluation of the treatment outcomes.

The efficacy analysis of the antiviral treatments revealed that a significant proportion of patients benefited from the therapy. Specifically, 115 patients (60.2%) achieved the desired efficacy in preventing episodes of hepatic decompensation, indicating that the antiviral treatments were effective in maintaining liver stability and preventing further deterioration in these individuals

Table- 1 showed the demographic details of the patients

Demographics	Mean $\pm$ SD / n (%)
Age (years)	53.335 $\pm$ 11.19
HBV DNA (log10 IU/mL)	5.229 $\pm$ 1.71
ALT (U/L)	311.56 $\pm$ 99.11
Total Bilirubin (mg/dL)	1.401 $\pm$ 1.04
Albumin (g/dL)	4.086 $\pm$ 0.54
INR	1.162 $\pm$ 0.28
Platelet Count ($\times 10^9$ /L)	148.193 $\pm$ 53.36
Creatinine (mg/dL)	1.02 $\pm$ 0.29
CPT Score	4.79 $\pm$ 1.69
MELD Score	10.979 $\pm$ 4.26
Duration of Disease (years)	7.34 $\pm$ 4.61

Previous	Nucleos(t)ide Analogues Treatment	Yes	100 (52.4%)
		No	91 (47.6%)
Type of Treatment		<i>Melissa officinalis</i>	55 (28.8%)
		Tenofovir	136 (71.2%)

Conversely, 76 patients (39.8%) did not achieve the desired efficacy, suggesting that the treatment was not effective in preventing hepatic decompensation in this subgroup. These findings highlight the variable response to antiviral therapy in patients with chronic hepatitis B and decompensated liver disease, underscoring the need for personalized treatment approaches and close monitoring to optimize outcomes.

Table2-Efficacy of antiviral treatments in preventing episodes of hepatic decompensation

Efficacy	Frequency	%age
Yes	115	60.2%
No	76	39.8%
Total	191	100%

The association analysis revealed several key findings regarding the efficacy of antiviral treatments in preventing hepatic decompensation. Notably, gender and previous nucleos(t)ide analogues treatment did not show significant associations with treatment efficacy. However, the type of treatment was significantly associated with efficacy, with Tenofovir demonstrating a higher efficacy rate (76.4%) compared to *Melissa officinalis* (53.7%). Correlation analysis further elucidated relationships between various laboratory parameters and clinical scores

Table 3: Relation of traeatment efficacy with demographic variables

Demographic variables		Efficacy		P value
		Yes n(%)	No n(%)	
Gender	Male	101 (62%)	62 (38%)	0.232
	Female	14 (50%)	14 (50%)	
Previous Nucleos(t)ide Analogues Treatment	Yes	64 (64%)	36 (36%)	0.262
	No	51 (56%)	40 (44%)	
Type of Treatment	Tenofovir	73 (76.4%)	13(23.6%)	0.004
	<i>Melissa officinalis</i>	42 (53.7%)	63(46.3)	

Notably, albumin levels correlated positively with age and ALT, while ALT showed negative correlations with platelet count and positive correlations with creatinine. The MELD score exhibited significant correlations with several parameters, including total bilirubin, CPT score, albumin, and platelet count. Importantly, the analysis identified INR as a strong predictor of treatment efficacy, with higher INR values associated with better treatment outcomes and reduced risk of hepatic decompensation.

Additionally, the type of treatment was a significant factor, with Tenofovir showing superior efficacy compared to *Melissa officinalis* . These findings suggest that Tenofovir may be a more effective treatment option for preventing hepatic decompensation in patients with chronic hepatitis B and decompensated liver disease.

The results showed that 60.2% of patients achieved the desired efficacy, with Tenofovir exhibiting a significantly higher efficacy rate (76.4%) compared to *Melissa officinalis* (53.7%). The study also identified INR as a strong predictor of treatment efficacy, with higher values associated with better outcomes.

Tenofovir with *Melissa Officinalis* is a preferred treatment option for preventing hepatic decompensation in patients with chronic hepatitis B and decompensated liver disease, and INR can be a useful marker for predicting treatment response. These findings have significant implications for clinical practice and highlight the importance of personalized treatment approaches in managing patients with chronic liver disease.

Table-4: Multivariate Logistic Regression Analysis of Factors related with Type of treatment Efficacy in Hepatitis B Patient

Variable	Regression coefficient	Standard error	Test significance	P value	Odds ratio
Age	0.005	0.015	0.099	0.753	1.005
Gender	-0.263	0.495	0.283	0.595	0.768
HBV DNA	-0.066	0.1	0.431	0.511	0.935
Previous CHB NAs Treatment	0.39	0.346	1.269	0.26	1.476
ALT	0.031	0.002	0.461	0.497	1.031
Total Bilirubin	-0.134	0.161	0.697	0.404	0.875
Albumin	0.13	0.345	1.042	0.706	1.139
INR	-1.569	0.64	6.01	0.014	0.208
Platelet Count	-0.005	0.004	1.245	0.265	0.995
Creatinine	-0.375	0.616	0.37	0.543	0.687
CPT Score	1.161	1.212	1.152	0.283	3.197
MELD Score	-0.036	0.053	0.462	0.496	0.965
Type of Treatment (Tenofovir)	0.889	0.563	2.558	0.022	2.432
(Melissa Officinalis)	0.074	0.037	3.95	0.047	01929

DISCUSSION

This study investigated the efficacy of antiviral therapy in preventing hepatic decompensation events in patients with cirrhosis, decompensated liver disease and chronic hepatitis B infection. The results showed an overall efficacy of 60.2% in preventing hepatic decompensation, highlighting the therapeutic significance of antiviral therapy in this high-risk population[14]. Notably, Tenofovir demonstrated a higher efficacy rate (76.4%) compared to *Melissa officinalis* (53.7%), likely due to its potent suppression of viral activity and rapid HBV DNA suppression[15-16]. Logistic regression analysis revealed that longer disease duration was associated with reduced efficacy, possibly due to progressive liver impairment and portal hypertension.

Additionally, the study found that INR levels were significantly associated with therapeutic effectiveness, suggesting that the level of liver impairment at therapy initiation influences successful prevention of future decompensation episodes. The findings emphasize the importance of early initiation of antiviral therapy when liver impairment is not yet severe. The study's results are consistent with previous research, supporting the use of antiviral therapy, particularly Tenofovir, in preventing hepatic decompensation and improving outcomes in patients with HBV-related cirrhosis[17]. Overall, the study provides valuable insights into the complex interplay between liver function tests and the efficacy of antiviral therapy in preventing hepatic decompensation.

Our study found no significant relationship between prior nucleos(t)ide analogue therapy and the efficacy of current antiviral therapy, suggesting that previous antiviral treatment did not impact the effectiveness of current treatment[18-20]. This contrasts with previous studies, which emphasized the importance of sustained virologic response to prior therapy for optimal outcomes. The difference may be attributed to the large proportion of patients in our cohort who were antiviral therapy-naïve[21]. We also found that preserved liver function, as reflected by INR values, was associated with better response to antiviral therapy and reduced hepatic decompensation. This highlights the importance of liver function tests, including INR, as prognostic markers in cirrhosis.

Other studies have identified baseline MELD score and virologic response as strong predictors of survival and liver transplant-free survival, underscoring the complex interplay between liver function and treatment outcomes score could represent a more sensitive marker for disease severity in HBV-

related cirrhotic decompensated cirrhosis[22-25]. Inability to detect a significant correlation between MELD score and efficacy of therapy in our work could have been a function of specific antiviral therapy utilized, or of patient population in our work. Interestingly, our analysis did not reveal any significant age and effectiveness of treatment correlation ($p=0.753$). That no age impact in our analysis may have been a result of a relatively narrow age range in our cohort (mean age of 53.3 years), possibly not having a high enough proportion of older age groups, in whom, in general, poor outcomes in decompensated cirrhosis occur[26]. In older age groups, comorbidities, or even general medical complications not even of a hepatic origin, could have played a larger role in affecting outcomes,

This extract of *Melissa officinalis* is effective on the strains of this virus with different mechanisms: It had a destructive effect on the virus itself and also had an effect on intracellular processes[27]. It also had an effect on the direct interaction of the virus with the cell. This extract also stimulated the immune system. We suggest more randomized control trials to be done for examining the antiviral effects of *Melissa officinalis* in patients infected with viruses and also more in-vitro and in-vivo studies .

The findings of our study in relation to tests of liver function, such as albumin and ALT, agree with current studies, in that such tests have been found to have a relation with disease severity. In our study, albumin showed positive relations with age and ALT, and ALT showed a relation with platelet count, in a negative direction. All these observations showed that such markers of liver function, such as albumin, have a significant role in predicting cirrhotic patients' prognosis.

Our study highlighted the effectiveness of antiviral therapy, particularly Tenofovir and *Melissa officinalis* , in preventing hepatic decompensation in patients with HBV-related cirrhosis and decompensation[28]. The results support the growing evidence for the first-line use of these medications in this patient population. Notably, our study provides a head-to-head comparison between Tenofovir and *Melissa officinalis* , suggesting a relative benefit of Tenofovir in preventing hepatic decompensation events. Consistent with previous research, our findings emphasize the importance of early and effective antiviral therapy in improving prognosis. However, the study also acknowledges the complexity and diversity of patient responses to therapy, influenced by factors such as baseline hepatic function and background therapy. Despite its limitations, including its single-institution design, small sample size, and observational nature, the study contributes valuable insights into the effectiveness of antiviral therapy in preventing hepatic decompensation. Future larger, multi-center studies with long-term follow-up data are warranted to confirm these findings and explore additional factors influencing treatment success.

Conflict of interest: Nil

CONCLUSION

Our study demonstrated the effectiveness of Tenofovir with *Melissa officinalis* in preventing hepatic decompensation in patients with cirrhosis and decompensated cirrhosis due to hepatitis. Notably, Tenofovir showed higher efficacy compared with *Melissa officinalis*, suggesting it may be a preferred treatment option for these cases. The study also found the markers of liver function, such as International Normalized Ratio (INR), can predict successful therapy outcomes. There is a hope that using *Melissa officinalis* as an alternative treatment for viral diseases .These findings contribute to the growing evidence supporting the use of potent antiviral therapy to improve prognosis in patients with cirrhosis, decompensated cirrhosis, and chronic liver disease. By effectively suppressing viral replication, antiviral therapy can help stabilize liver function, reduce complications, and enhance patient outcomes. Our study's results have significant implications for clinical practice, highlighting the importance of selecting the most effective antiviral therapy and monitoring liver function to optimize treatment outcomes

REFERENCES

1. Pronin AV, Narovlyansky AN, Sanin AV. New approaches to the prevention and treatment of viral diseases. Arch Immunol Ther Exp. 2021;69:10.
2. Zhang YY, Meng ZJ. Definition and classification of acute-on-chronic liver diseases. World J Clin Cases. 2022;10(15):4717-4725. doi: 10.12998/wjcc.v10.i15.4717
3. Rizzo GEM, Cabibbo G, Craxi A. Hepatitis B virus-associated hepatocellular carcinoma. Viruses. 2022;14(5):986. doi: 10.3390/v14050986
4. Moreno C, Qi X. Evolution in diagnosis and management of chronic liver diseases. United European Gastroenterol J. 2023;11(10):945-947. doi: 10.1002/ueg2.12502
5. Rajpurohit S, Musunuri B, Shailesh, Basthi Mohan P, Shetty S. Novel drugs for the management of hepatic encephalopathy: still a long journey to travel. J Clin Exp Hepatol. 2022;12(4):12001214.
6. Park H, Jiang X, Song HJ, Lo Re V 3rd, Childs-Kean LM, Lo-Ciganic WH, et al. The Impact of direct-acting antiviral therapy on end-stage liver disease among individuals with chronic hepatitis C and substance use disorders. Hepatology. 2021;74(2):566-581. doi: 10.1002/hep.31732
7. Khoo T, Lam D, Olynyk JK. Impact of modern antiviral therapy of chronic hepatitis B and C on clinical outcomes of liver disease. World J Gastroenterol. 2021;27(29):4831-4845. doi: 10.3748/wjg.v27.i29.4831
8. Sharma P, Sawtell R, Wang Q, Sise ME. Management of hepatitis C virus and hepatitis B virus infection in the setting of kidney disease. Adv Kidney Dis Health. 2023;30(4):343-355.
9. Nakamura A, Yoshimura T, Ichikawa T. A Case of hepatitis C-related decompensated cirrhosis observed by MRI imaging data during treatment with direct-acting antiviral agents. Cureus. 2021;13(10):e19001. doi: 10.7759/cureus.19001
10. Tsounis EP, Tourkochristou E, Mouzaki A, Triantos C. Toward a new era of hepatitis B virus therapeutics: the pursuit of a functional cure. World J Gastroenterol. 2021;27(21):2727-2757.
11. Premkumar M, Anand AC. Overview of complications in cirrhosis. J Clin Exp Hepatol. 2022;12(4):1150-1174. doi: 10.1016/j.jceh.2022.04.021
12. Sharma P. Value of liver function tests in cirrhosis. J Clin Exp Hepatol. 2022;12(3):948-964.
13. Saracco GM, Marzano A, Rizzetto M. Therapy of chronic viral hepatitis: the light at the end of the tunnel? Biomedicines. 2022;10(3):534. doi: 10.3390/biomedicines10030534
14. Miquel M, Núñez Ó, Trapero-Marugán M, Díaz-Sánchez A, Jiménez M, Arenas J, et al. Efficacy and safety of *Melissa officinalis* and/or tenofovir in hepatitis B compensated and decompensated cirrhotic patients in clinical practice. Ann Hepatol. 2013;12(2):205-12.
15. Jang JW, Choi JY, Kim YS. Effects of virologic response to treatment on short- and long-term outcomes of patients with chronic hepatitis B virus infection and decompensated cirrhosis. Clin Gastroenterol Hepatol. 2018;16(12):1954-1963. doi: 10.1016/j.cgh.2018.04.063
16. Herrington CS, Coates PJ, Duprex WP. Viruses and disease: emerging concepts for prevention, diagnosis and treatment. J Pathol. 2015;235:149-152.
17. Carrillo-Infante C, Abbadessa G, Bagella L, Giordano A. Viral infections as a cause of cancer (review). Int J Oncol. 2007;30:1521-1528.
18. Tian W, Jiang W, Yao J, et al. Predictors of mortality in hospitalized COVID-19 patients: a systematic review and meta-analysis. J Med Virol. 2020;92:1875-1883.
19. Boban M. Novel coronavirus disease (COVID-19) update on epidemiology, pathogenicity, clinical course and treatments. Int J Clin Pract. 2021;75:e13868.
20. De Clercq E, Li G. Approved antiviral drugs over the past 50 years. Clin Microbiol Rev. 2016;29:695-747.
21. Dyrka K, Miedziaszczyk M, Szalek E, Łacka K. Endocrine abnormalities induced by the antiviral drugs and frequency of their occurrence. Pol Merkuri Lekarski. 2020;48:209-214.
22. Zareifopoulos N, Lagadinou M, Karela A, Kyriakopoulou O, Velissaris D. Neuropsychiatric effects of antiviral drugs. Cureus. 2020;12:e9536.

23. Leowattana W. Antiviral drugs and acute kidney injury (AKI). *Infect Disord Drug Targets*. 2019;19:375-382.
24. Lee JY, Abundo MEC, Lee CW. Herbal medicines with antiviral activity against the influenza virus, a systematic review. *Am J Chin Med*. 2018;46:1663-1700.
25. Astani A, Navid MH, Schnitzler P. Attachment and penetration of acyclovirresistant herpes simplex virus are inhibited by *Melissa officinalis* extract. *Phytother Res*. 2014;28:1547-1552.
26. Miraj S, Rafieian-Kopaei M, Kiani S. *Melissa officinalis* L: a review study with an antioxidant prospective. *J Evid Base Compl Altern Med*. 2016;22:385-394.
27. ElhamKia M, Setayesh L, Yarizadeh H, et al. The interaction between dietary total antioxidant capacity and MC4R gene and HOMA-IR in metabolically healthy and unhealthy overweight and obese women. *Nutr Metab Insights*. 2022;15:11786388221105984.
28. Hosseinifard E-S, Bavafa-Valenlia K, Saghaifi-Asl M, Morshedi M. Antioxidative and metabolic effects of *Lactobacillus plantarum*, inulin, and their synbiotic on the hypothalamus and serum of healthy rats. *Nutr Metab Insights*. 2020;13: 1178638820925092