論　文　内　容　の　要　旨
Synopsis of Thesis

氏　名 Name	RAHMAN MD. ARIFUR
論文題名 Title	A Traditional Chinese Medicine, Maoto, Suppresses Hepatitis B Virus Production （伝統漢方麻黄湯は，HBVの産生を抑える）

論文内容の要旨

〔目　的(Purpose)〕

Worldwide, millions of people suffer from hepatitis B virus (HBV) infection, putting them at a high risk of death from liver cirrhosis and cancer. Although effective anti-HBV drugs have been developed, current drugs have some limitations, as most of them have a risk of significant side effects. Therefore, the discovery of safe and effective anti-HBV drugs is still needed. Natural compounds are considered sources of novel, safe and effective therapeutics. In these regards, we screened a library of Kampos, traditional herbal medicines, for suppression of HBV production.

〔方法ならびに成績(Methods/Results)〕

The library consisted of 41 Kampo extracts, provided by the University of Toyama. HepAD38.7 cells, a tetracycline-controlled HBV producing cell line, was incubated for 9 days with or without Kampo extracts in the tetracycline-negative (tet-off; virus production mode) condition. Cell viability was determined by an MTT assay. Anti-HBV activities were evaluated by qPCR of HBV DNA and an HBeAg ELISA in the soup. Results were further confirmed by additional cell lines such as HepG2-NTCP producing cell and Primary human hepatocytes (PHH).

We found that maoto reduced extracellular HBV DNA but not extracellular HBsAg during HBV infection, suggesting that it suppressed HBV production by interfering with HBV nucleocapsid incorporation into viral particles. We suggested the potential of maoto for increasing the efficacy of current anti-HBV drugs (i.e. Lamivudine; LV) when used in combination. Since the safety of maoto has been already confirmed, maoto can be considered a candidate anti-HBV agent if the effect is confirmed *in vivo*. Finally, we investigated the molecular mechanisms of how maoto suppressed extracellular HBV production by RNA-seq analysis of maoto-treated and untreated cells. We detected several up-regulated and down regulated genes however, we revealed that maoto reduced the expression of a host gene, *Tropomyosin β chain (TPM2)*, whose downregulation also suppressed HBV production, similarly to maoto. The results suggested TPM2 as a novel molecular target for the development of anti-HBV agents.

〔総　括(Conclusion)〕

Overall, maoto seems to be a unique candidate that targets a process different from those targeted by existing drugs and can enhance the anti-HBV activity of current drugs when used in combination.

[Format-H07]

論文審査の結果の要旨及び担当者

（申請者氏名）RAHMAN MD. ARIFUR

	(職)	氏　名
論文審査担当者	主　査　大阪大学教授	上田 路次
	副　査　大阪大学特任教授	松浦 善治
	副　査　大阪大学教授	塩田 達雄

論文審査の結果の要旨

Worldwide, millions of people suffer from hepatitis B virus (HBV) infection, putting them at a high risk of death from liver cirrhosis and cancer. Although effective anti-HBV drugs have been developed, current drugs have some limitations, as most of them have a risk of significant side effects. Therefore, the discovery of safe and effective anti-HBV drugs is still needed.

In this study, we screened a library of Kampos, traditional herbal medicines, for suppression of HBV production. Among them, we found that maoto reduced extracellular HBV DNA production but not extracellular HBsAg secretion during HBV infection, suggesting that it suppressed HBV production by interfering with HBV nucleocapsid incorporation into viral particles. Furthermore, we revealed that maoto reduced the expression of a host gene, Tropomyosin beta chain (TPM2), whose downregulation also suppressed HBV production, similarly to maoto. Since the safety of maoto has been already confirmed, maoto can be considered a candidate anti-HBV agent if the effect is confirmed in vivo. In addition, our findings also suggest TPM2 as a novel molecular target for the development of anti-HBV agents.

Thus, this is the first report to show maoto from a Kanpo library of natural compounds, as an effective anti-HBV drug and that TPM2 had some role on the effect and deserves Ph.D. degree.