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# Interaction between oseltamivir and herbal medicines used for treating avian influenza

## Key Messages

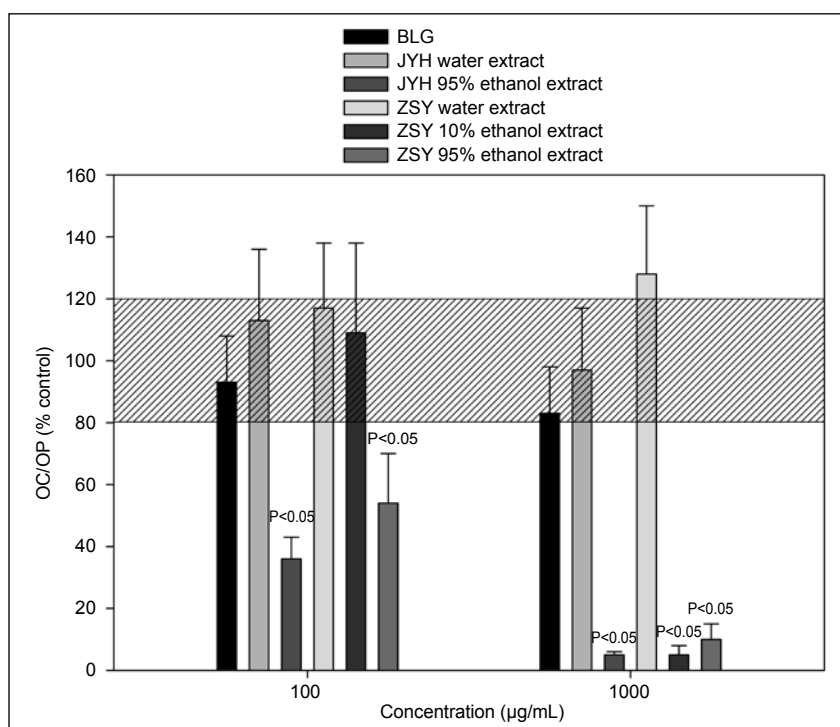
1. In vitro studies were used to investigate the effect of various herbal medicines on the activity of drug-metabolising enzymes, whereas a PBPK model was used to study the interaction between oseltamivir (Tamiflu) and herbal medicines.
2. The biochemical and molecular biological basis of drug-herb interactions were studied by determining the effect of herbal extracts on cellular redox states and gene expression profiles.
3. Herbal extracts may affect oseltamivir treatment in rats. The drug-herb interaction may be related either to the metabolism or uptake of the drug by different tissues. Further studies are necessary to determine whether such interactions also occur in humans.

## Introduction

Oseltamivir (Tamiflu) is a cyclopentane neuraminidase inhibitor for treatment of influenza viruses, including the H5N1 avian influenza strain encountered in Hong Kong.<sup>1,2</sup> Oseltamivir is a safe drug with wide margin of safety. It is tolerable in single doses of up to 1000 mg (14 mg/kg/day) for a 70 kg adult and may be given as 500 mg twice daily. Commonly it is administered as the prodrug, oseltamivir phosphate (OP). It is then biotransformed into its active metabolites oseltamivir carboxylate (OC) through ester hydrolysis. Recent reports have shown a strain of Tamiflu-resistant virus.<sup>3-5</sup> In view of this, Chinese herbal medicine was added for combating avian influenza. Herbal medicine that contains *Flos Lonicerae* (金銀花, JYH) and *Folium Perillae* (紫蘇葉, ZSY) and over-the-counter preparation such as *Radix isatidis* (板藍根, BLG) are commonly taken by the public to combat influenza symptoms. The present study investigated a possible interaction between oseltamivir and these herbal extracts and assessed the safety of their combined use.

## Methods

This study was conducted from December 2006 to February 2009 using both in vitro (n=6) and in vivo (n=4) samples. It was divided into three parts. In the first part, in vitro studies were used to investigate the effect of various herbal medicines on



**Fig 1. Suppression of plasma carboxylesterase activity on converting oseltamivir phosphate (OP) to oseltamivir carboxylate (OC) following addition of different concentrations (100 and 1000 µg/mL) of herbs**  
Each value represents the means and SD of four rats. Grey area indicates a ±20% variation range in control value of 100%.

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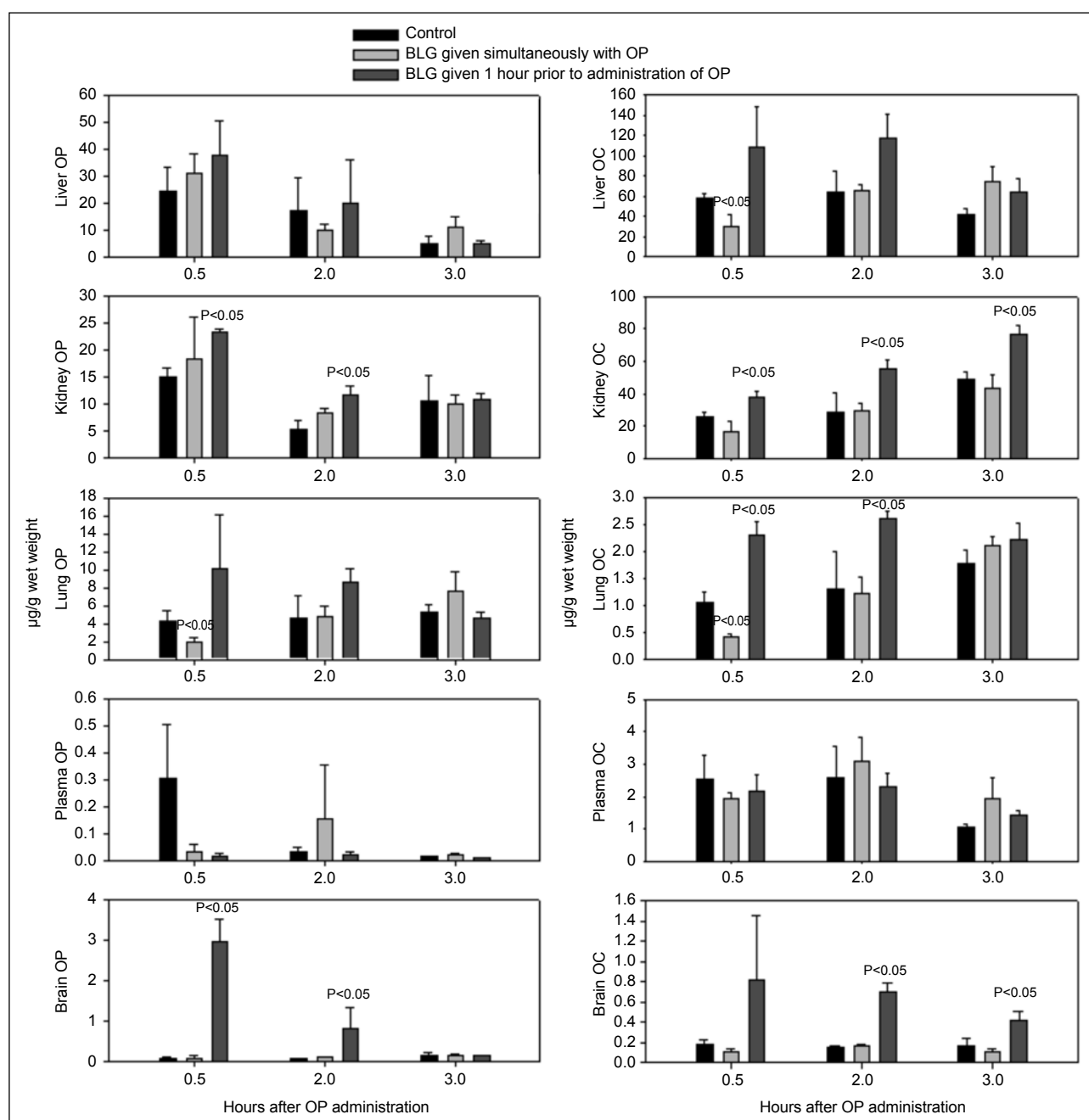
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the activity of OP-metabolising enzymes, which include the carboxylesterase (CE) that activates OP to OC, and CYP450 isoenzymes 1A1, 2C9, 2C19, and 3A4 that metabolise many western drugs. In the second part, a PBPK model was derived to measure tissue distribution of OP and OC and to study any possible interaction between OP and the herbal medicines. In the third part, the biochemical and molecular biological basis of drug-herb interactions was investigated by determining the effect of several herbal extracts (JSY and JYH) on cellular redox states and gene expression profiles. Instruments used included spectrofluorometers, cell culture facilities, high-pressure liquid chromatography, LC-MS-MS, and PCR-microarray analysers.

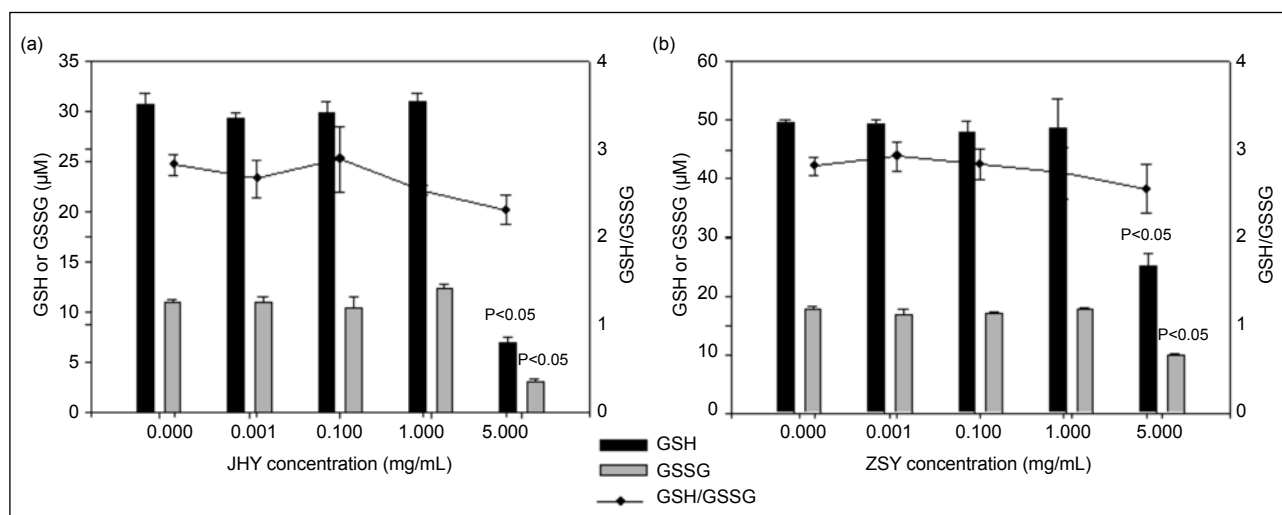
## Results

At high concentration (1 mg/mL), BLG exerted only a slight inhibition on carboxylesterase, whereas JYH and ZSY could significantly suppress the activity of this enzyme (Fig 1). Therefore, BLG was selected for the subsequent animal study.

The kinetic of distribution of OP and OC in various rat tissues was determined by measuring the levels of OP and OC. Most OP and OC were detected in the liver and kidney, with very small amount in the plasma. The OP and OC levels peaked at 2 h following administration. At 6 hr, OP



**Fig 2. Levels of oseltamivir phosphate (OP) and oseltamivir carboxylate (OC) in rat liver, kidney, lung, plasma, and brain at 0.5, 2, and 3 hours following exposure of OP (50 mg/kg) with *Radix isatidis* (板藍根, BLG) [0.4 g/kg].** Each value represents the mean and SD of three rats.



**Fig 3. Levels of GSH, GSSG, and GSH/GSSG ratio in the HepG2 cells following exposure to the water extract of (a) *Flos Lonicerae* (金銀花, JYH) or (b) *Folium Perillae* (紫蘇葉, ZSY) for 24 hours.**

and OC levels had decreased. These results fitted with the PBPK model constructed in our laboratory. In the presence of BLG, changes were detected in different tissues, with the lung being most affected. When BLG was administered simultaneously, the OC level was significantly reduced during the initial 3 hr. However, if BLG was administered 1 hr prior to oseltamivir administration, the lung OC content was significantly increased. According to the PBPK model, the change may be modified by altering the kinetics of uptake. Thus, BLG may affect the uptake rates of OP and OC in tissues such as the lung. Similar changes were also observed in the brain and kidney but not reflected in the plasma (Fig 2). The results were tested in a PBPK model using a simulation program AcslXtreme OptStat (Aegis Simulation). By fitting the tissue data on the PBPK model, interference with the uptake of OP may be the basic action of BLG.

Although the kinetic interaction effects of JYH and ZSY with oseltamivir was not investigated, the action of these extracts in cultured cells model was studied. In human HepG2 cells, the water extracts of both JYH and ZSY could cause cell death only at very high concentrations (>1 mg/mL for 24 h). At such concentrations, JYH was able to cause depletion of glutathione (Fig 3) and suppress the activity of cytochrome P450 isoenzymes 1A1, 2C9, 2C19, and 3A4.

## Discussion

In the rat model, simultaneous administration of BLG and OP orally may reduce the level of OC in lung tissues and thus reduce antiviral activity. Pre-treatment with BLG may help improve oseltamivir uptake in the lung during the initial 3 hr. Nevertheless, this may also increase OC levels in the brain and kidney, but these changes were not reflected in the plasma. High concentrations of water extracts of JYH and ZSY may affect the activity of several CYP450 isoenzymes. This suggested that they should not be taken

simultaneously with drugs that are metabolised by these enzymes (eg Panadol).

Herbal extracts may affect oseltamivir treatment in rats. The action may be related either to its metabolism or to the uptake of the drug by different tissues. Further studies are necessary to determine whether such drug-herb interactions also occur in humans.

## Acknowledgements

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