

## Introduction

- It is estimated that 20–35% of prescribed medication users take in addition herbs and other related products.
- Supplementation of pharmacotherapies with herbal products in patients has attracted much attention.
- This is a result of increasingly reported health consequences of herb–drug interactions (HDI) in both case reports and controlled clinical investigations.
- Although several studies on pharmacokinetic herb–drug interactions (HDI) have been conducted in healthy volunteers, there is large uncertainty on their validity.
- A qualitative and meta-analysis was performed to establish the clinical importance of these interaction studies.

## Study Objectives

- The primary objective was to determine the changes in AUC and clearance of midazolam in the presence of herbal products using meta-analysis.
- In addition, meta-analysis was conducted for other pharmacokinetic parameters such as half-life ( $t_{1/2}$ ), maximum plasma concentration ( $C_{max}$ ) and time to attain the maximum plasma concentration ( $t_{max}$ ) as secondary objectives.
- Influence of covariates: age, weights, dosage and duration of treatments and publication bias on pharmacokinetic indices were assessed.

## Study Protocol

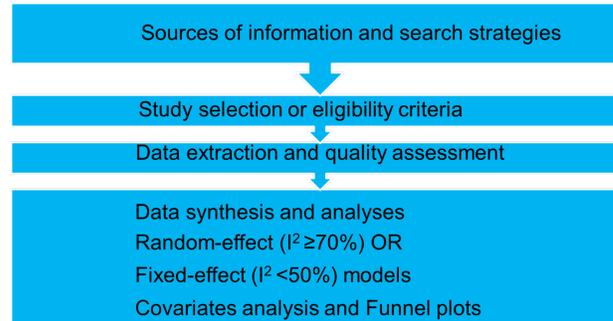


Figure 1: Scheme of study protocol.

## Study Results

### Selection of studies included in the review and meta-analysis

- Forty-three articles were included in both the qualitative and meta-analysis.
- The qualitative analysis consisted of 32 articles and the remaining eleven articles were included in the meta-analysis.

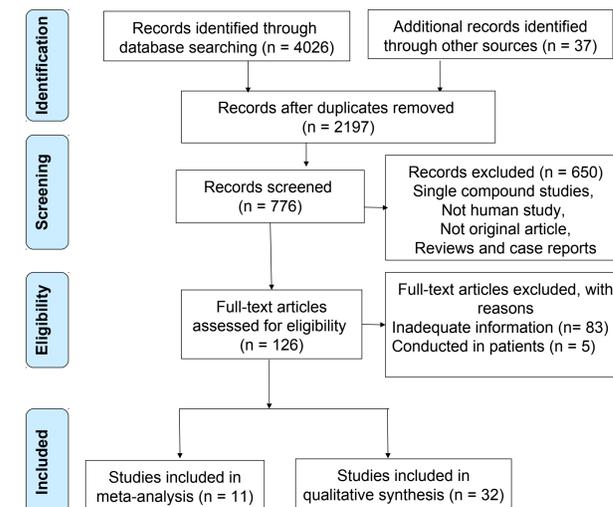


Figure 2: Flow diagram for selecting related articles

## References

- Awortwe C, Bruckmüller H, Cascorbi I. Interaction of herbal products with prescribed medications: A systematic review and meta-analysis. *Pharmacol Res.* 2019; 141: 397-408.
- Awortwe C, Makiwane M, Reuter H, Müller C, Louw J, Rosenkranz B. Critical evaluation of causality assessment of herb–drug interactions in patients. *Br J Clin Pharmacol.* 2018; 84(4): 679-693.

## Influence of herbs on AUC of midazolam

A forest plot indicated that St. John's wort (SJW) significantly decrease AUC of midazolam  $-22.5$  ng/mL (95%CI:  $-27.2$  to  $-17.8$  ng/mL;  $p < 0.0001$ ).

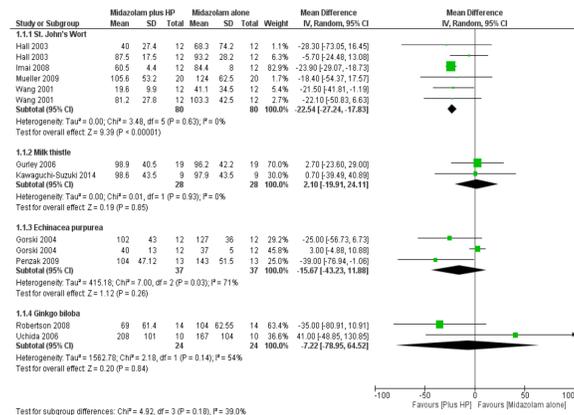


Figure 3: Forest plot showing mean difference in AUC of midazolam with or without herbal products.

## Influence of herbs on CL of midazolam

SJW and *Echinacea purpurea* (EP) increased the clearance of midazolam by 26.9 L/h (95%CI: 7.5–46.4 L/h;  $p=0.007$ ) and 11.9 L/h (95%CI: 2.8–21.0 L/h;  $p=0.01$ ), respectively.

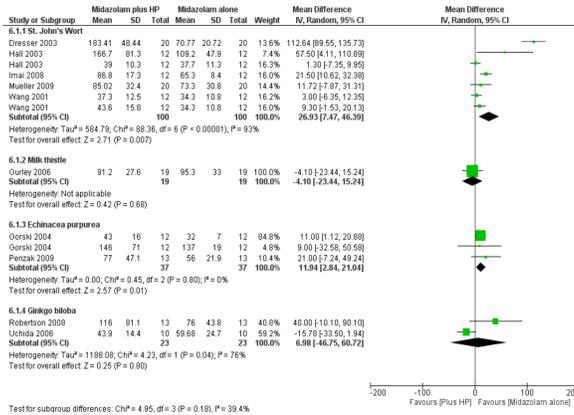


Figure 4: Forest plot showing mean difference in clearance of midazolam with or without herbal products.

## Influence of herbs on $t_{1/2}$ of midazolam

SJW and EP decreased half-life of midazolam by  $-0.33$  h (95%CI:  $-0.43$  to  $-0.22$  h;  $p < 0.00001$ ) and by  $-1.6$  h (95%CI:  $-3.1$  to  $-0.1$  h;  $p=0.04$ ), respectively.

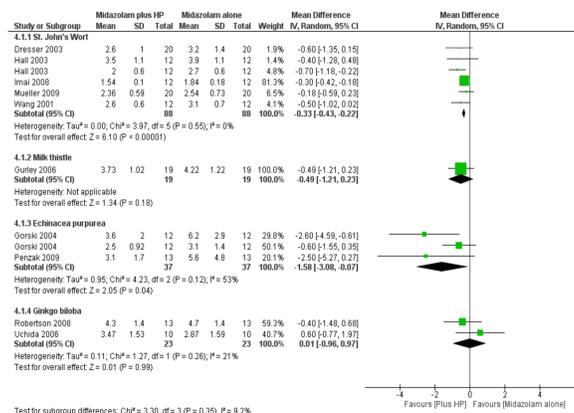


Figure 5: Forest plot showing mean difference in half-life of midazolam with or without herbal products.

## Influence of herbs on $C_{max}$ of midazolam

The peak midazolam serum concentration ( $C_{max}$ ) decreased by  $-5.8$  ng/mL (95%CI:  $-9.6$  to  $-2.0$  ng/mL;  $p=0.003$ ) in the presence of SJW with a statistical heterogeneity of  $I^2=75\%$  and  $p=0.003$ .

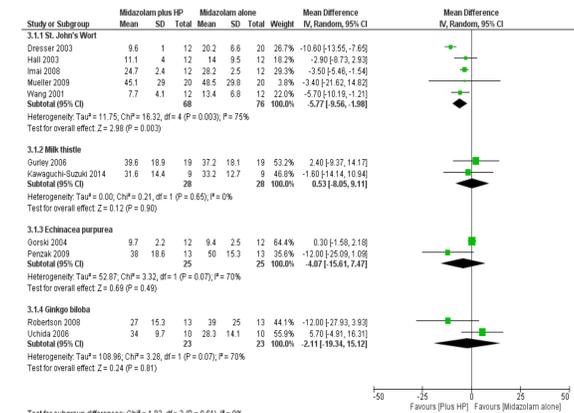


Figure 6: Forest plot showing mean difference in  $C_{max}$  of midazolam with or without herbal products.

## Influence of herbs on $t_{max}$ of midazolam

None of the herbal products (EP, SJW, Ginkgo biloba and Milk thistle) affected the time to achieve maximum plasma or serum concentration ( $t_{max}$ ) of midazolam.

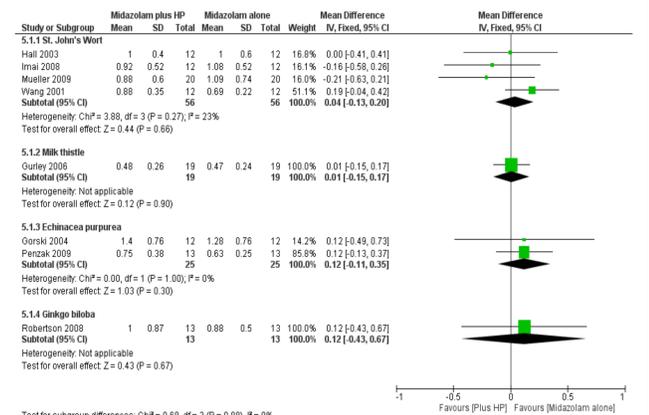


Figure 7: Forest plot showing mean difference in  $t_{max}$  of midazolam with or without herbal products.

## Covariates analysis and Publication bias

- $C_{max}$  of midazolam was influenced by age (QM (df (1))=15.60;  $p < 0.01$ ).
- Further subgroup analysis confirmed age as significant covariate (QM [df (1)]=11.84;  $p < 0.01$ ) on the decrease in  $C_{max}$  of midazolam by SJW.

AUC,  $C_{max}$  and  $t_{max}$  outcomes indicated no publication bias with a symmetrical funnel plots.

A hypothetical imputation showed four missing studies for both clearance and  $t_{1/2}$  (Fig 7B–C).

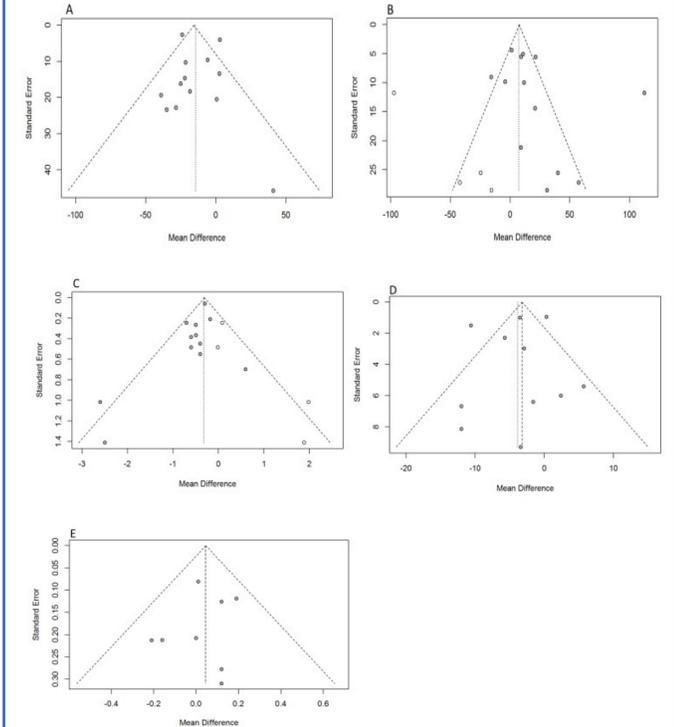


Figure 8: Funnel plot of standard error by mean difference. AUC (A), Clearance (B), half-life (C),  $C_{max}$  (D) and  $t_{max}$  (E). Note: closed circles=actual publication; open circles=hypothetical omitted study.

## Conclusions

- The study findings suggest that St. John's Wort is not safe to be taken concomitantly with prescribed medications that are substrates for CYP3A4.
- Although *Echinacea purpurea* showed a moderate effect on pharmacokinetic indices of midazolam, its likelihood to cause interaction of clinical importance with prescribed medications cannot be ignored.
- Our studies show that meta-analyses of clinical studies are important in the area of natural products

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