# St. John's Wort Enhances the Platelet Inhibitory Effect of Clopidogrel in Clopidogrel "Resistant" Healthy Volunteers

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## INTRODUCTION

We previously demonstrated that platelet aggregation inhibition by clopidogrel inversely correlated with the metabolic activity of the hepatic cytochrome P450 (CYP) 3A4 isoenzyme. Rifampin, co-administered with clopidogrel, effectively converted volunteers who were known clopidogrel non- and low-responders (clopidogrel "resistant") to responders, measured by ex vivo platelet aggregometry.[1] Rifampin, an inducer of the hepatic CYP3A4 isoenzyme enhanced the platelet anti-aggregatory effect of clopidogrel.

St John's Wort (SJW), an herb, with the constituent hyperforin, is a potent ligand for the nuclear steroid pregnane X receptor (PXR) response element[2] that induces hepatic CYP3A4 enzymatic activity and increases the efficacy of drugs that are dependent on CYP3A4 for their metabolic activation.[3] We thus hypothesized that SJW would also enhance the platelet inhibitory effect of clopidogrel by induction of CYP3A4.

## METHODS

- Six healthy clopidogrel "resistant" subjects were recruited. "Resistance" was defined as a relative decrease in platelet aggregation < 30% measured by Plateletworks ™ test (Helena Laboratories, Beaumont, TX) whole blood aggregometry using 20μM ADP at 2, 4, and 6 hours after clopidogrel 450 mg. (Blue bars)
- After a 14 day washout period, subjects were treated with SJW 300 mg (Nature's Way, standardized to 3% hyperforin), three times daily for 14 days.
- Platelet aggregation was again measured before clopidogrel and 2, 4, and 6 hours after clopidogrel 450 mg. (Yellow bars)
- Erythromycin breath test was subsequently measured in the latter two subjects before, after 14 days of SJW, and 4 hours after SJW + clopidogrel 450 mg.

## RESULTS

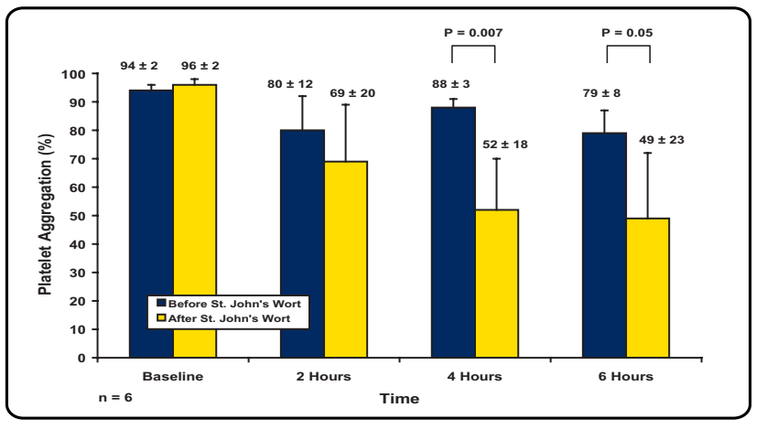


**Figure 1**

Conversion of clopidogrel non-responders to responders at 4 and 6 hours after SJW detected by point-of-care whole blood aggregometry.

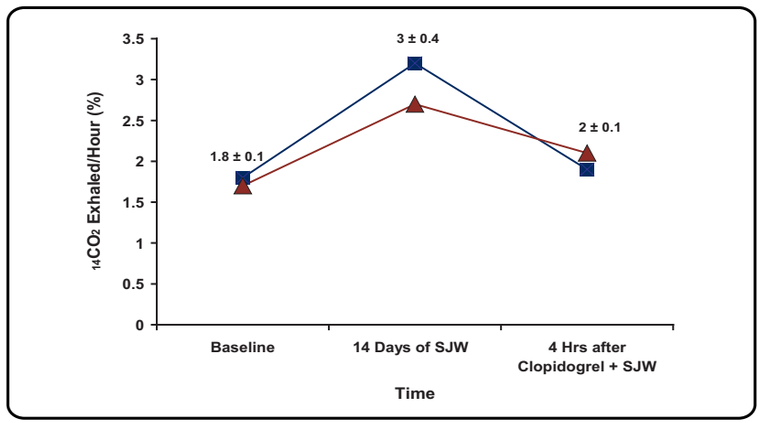


**Figure 2**

Hepatic CYP3A4 metabolic activity measured by erythromycin breath test increased *greater than* 1.5 fold after SJW. Clopidogrel utilizes CYP3A4 for its metabolic activation.

## CONCLUSION

1. SJW increases CYP3A4 activity, converting clopidogrel non- and low-responders to clopidogrel responders.
2. Clopidogrel utilizes CYP3A4 for its metabolic activaton and is a substrate inhibitor of CYP3A4.
3. Herb-drug interactions are pharmacologically important.

## REFERENCES

1. Lau et al., Circulation 2004; 109; 166 - 171.
2. Watkins et al., Biochemistry 2003; 42; 1430 - 1438.
3. Zhou et al., J. Psychopharmacol 2004; 18; 262 - 276.

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