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**Master Thesis Defense**

Entitled

*IN-VITRO ANALYSIS OF POTENTIAL AUTOPHAGY MEDIATED SAFRANAL-SORAFENIB  
COMBINED EFFECT ON HEPATOCELLULAR CARCINOMA*

by

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Abstract

HCC is one of the most commonly occurring cancers worldwide. The risk factors include obesity, hepatitis, alcoholism, smoking etc. The current treatment options are limited, not economical and easily accessible in all parts of the world, especially in cases with increased HCC incidence. Sorafenib, a multikinase inhibitor, is one of the first FDA approved drugs for HCC. But drug resistance and cancer relapse are a common drawback for this treatment. The need for better treatment is crucial now more than ever. The use of saffron as a therapeutic compound is not a novel concept. It has been long used as an analgesic, anti-inflammatory and anti-spasmodic in folk medicine. Recently, saffron and its constituents have shown anti-cancer properties across different cancers through different mechanisms. In this study, Safranal was tested against the hepatocellular carcinoma cell line (HepG2) for its effectiveness on cell viability and autophagy. The cells exhibited a decreased survival on treatment with Safranal which induced autophagy. This was confirmed by SDS-PAGE followed by western blot showing an increase in the expression of the major autophagic protein markers such as Beclin-1 and Atg 12, as well as by microscopic analysis for phagosome formation. Moreover, the combination of Safranal with Sorafenib showed antagonistic effect on Safranal inhibiting cell viability. The effect of Safranal and Sorafenib and their combination on the canonical kinases, AKT and ERK1/2, controlling the proliferative and the survival pathways, respectively was also investigated. Safranal had no effect on AKT expression level but drastically inhibited the phosphorylated form of AKT which is consistent with the inhibition of cell survival and the induction of autophagy. These results have provided with a possibility of Safranal being an effective chemotherapeutic against HCC. The combination treatment led to more complex observations that require further investigation in the future. Also, Safranal's effect on other cancerous cell lines and the other possible mechanisms by which Safranal affects HCC can be potential areas to broach in the future.

**Keywords:** Hepatocellular Carcinoma, Sorafenib, Safranal, Combination therapy, Autophagy.