

UNIVERSITI TEKNOLOGI MARA

**THE EFFECT OF *Tinospora crispa*
CRUDE METHANOLIC EXTRACT
ON HEPATOMA G2 CELL LINE
AND WISTAR RATS INSULIN
RESISTANCE MODEL**

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of the requirements for the degree of
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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Postgraduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

Sedentary and unhealthy lifestyles can contribute to the occurrence of metabolic diseases like insulin resistance (IR), diabetes, obesity and some types of cancer. *Tinospora crispa* is a significant herb in Malaysia, particularly in treating metabolic diseases have been addressed in many studies but the schematic of the signalling mechanism of both apoptosis and insulin resistance enhancement have not been revealed yet. Therefore, the aims of the study are to investigate the effect on insulin enhancement and apoptosis-related to the insulin resistance condition through *in-vitro* and *in-vivo* models. *In-vitro* analysis was performed using established insulin resistant liver cancer (IR-HepG2) cells model. The results exhibited a reduced glucose uptake in IR-HepG2 cells measured with radiolabelled 2-deoxyglucose (2DG) assay. Conversely, the reduction was reversible after treatments with *T. crispa*-CME in dose-dependent manner. *T. crispa*-crude methanolic extract (CME) restored the glucose uptake by upregulating the protein expression of InsR- β , GADPH, p-IRS and GLUT4. Simultaneously, the antiproliferative effect of *T. crispa*-CME was exhibited through apoptosis, thus inhibit the uncontrolled growth of IR-HepG2 by reducing the expression of IGF-1R and BCL-2. IGF-1R overexpression in IR-HepG2 impaired insulin-induced AKT phosphorylation thus inactivated glucose intake through GLUT4. In the meantime, apoptosis was induced via increment of pro-apoptosis protein expressions of Bad, caspases 8,-9 and -3. *In-vivo* analysis, Wistar rats was divided into four groups: a normal control (NC); high fat diet control (HFD); a *T. crispa* treatment group fed with high fat diet (HFDTC), and an Orlistat treatment group fed with high fat diet (HFDO). The respective groups were obesity-induced for eight weeks then administered with *T. crispa* crude extract into respective groups at a single dose of 2000mg/kg/b.w for continuously 28 days. The treatment with *T. crispa* had shown a significantly reduced body weight, blood glucose, adiposity index serum levels, liver enzymes, lipid, resistin, and leptin hormones. The hyperinsulinemia condition and C-peptide hormones restored to the normal stage. The histological examination of the liver treated with *T. crispa* crude extract did not show evidence of cells toxicity. *T. crispa*-CME has demonstrated insulin sensitivity enhancement by exhibiting an upregulation of InsR- β protein, which restored the glucose uptake in IR-HepG2 cancer cell lines. IGF-1R protein was downregulated, consequently induced apoptosis in IR-HepG2 cells. Our finding suggested that *T. crispa* crude extract has shown potential to improve glucose metabolism and correct compensatory hyperinsulinemia in insulin resistant conditions obese-induced Wistar rats. Determining the *T. crispa* treatment mechanism of insulin resistance in obesity and cancer would provide insight into future discoveries to yield herbal therapeutic benefits.

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