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Title:

Synthesis, characterization of novel derivative of Quercetin with thiourea [Z-1-(-2-(3′,4′-dihydroxyphenyl)-3,5,7-trihydroxy-4 *H* –chromen-4-ylidene) thiourea] and evaluation of its physiological effects on CCl_4 treated male laboratory rats

Abstract:

The present study was conducted in the Veterinary Medicine College /university of Basra to synthesis and characterize the antioxidant activity of the novel compound derivatives from condensation of quercetin with thaeourea yielded a novel Schiff base derivative of quercetin , **[Z-1-(-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4 *H* –chromen-4-ylidene) thiourea]** which is symbolized as **(QTU)** , The new compound (QTU) is synthesized in the biochemical laboratory, College of Pharmacy – University of Basra , characterized by IR, elemental analysis (CHN), ^{1}H-NMR and ^{13}C-NMR spectroscopy.

The experiment was divided into four parts:-

♦ **The first experiment (median lethal dose)**:

To determine the toxicity of the novel compound by intraperitoneal injection of adult laboratory male rats, and the median lethal dose (LD_{50}) was measured by the graphical method Miller and Tainter (1946) . It has been found to be 250 mg /kg of the body weight.

♦**The second experiment (antioxidant *In vitro* study of new compound)**: To study the antioxidant activity of the synthesized compound *in vitro* by comparing with the concentration of antioxidant activity of [2,2-Diphenyl-1-picrylhydrazyl] which coded DPPH.

♦**The third experiment (antioxidant *In vivo* study of new compound):** Thirty mature male rats range from (200-250) BW, are used to evaluate the protective effect of the novel compound against carbon tetrachloride (CCl_4) induced oxidative stress on rats selected randomly and divided into five groups (6 in each group) as following:

The first group of animals are injected intraperitoneally with 0.5ml of olive oil and considered as control group. The second group in which the animals are injected IP with 1/10 of LD_{50} of novel compound (QTU) alone its mean 25 mg/kg B.W. The third group of animals is injected IP with 1ml / kg. B.W of CCl_4. The Fourth and Fifth groups of the animals are injected IP with 1 ml/kg. B.W CCl_4, then after one hour they were injected IP with QTU (125 and 25 mg / kg B.W respectively).

The experiment lasted for four weeks. carbon tetrachloride treated rats exhibit a significant reduction ($P<0.05$) is observed in body weight whereas significant increase ($P<0.05$) in vital organs (liver ,kidney / testes) and increase ($P<0.05$) in leukocytes count, serum level of liver enzymes (ALT and AST, ALP), Lipid profile, total bilirubin level, urea, uric acid, MDA , whereas a significant reduction ($P<0.05$) was noted in RBCs count , hemoglobin concentration, hematocrit ratio and serum level of HDL-C, total protein level and antioxidant enzymes (GPx, SOD and catalase). ; and significant reduction ($P<0.05$) in sperm concentration, sperm motility percentage and live sperm had been noted in CCl_4 group. Moreover, histopathological changes in liver and testes have been noticed, CCl_4 induced changes are ameliorated by administration of synthesized compound (QTU).

♦ **<u>The fourth experiment (reproductive study of new compound)</u>:**

In this part of the experiment, 30 mature rats are used (20 female and 10 male). Females and males have been separated for the 16 days before the onset of the experiment to insure that the females had not been conceived. The male rats were divided into five groups as follow. The first group of animals are injected intraperitoneally with 0.5ml of olive oil and considered as control group. The second group in which the animals are injected IP 25 mg/kg B.W. The third group of animals were injected IP with 1ml/ kg. BW of CCl_4. The Fourth and Fifth groups of the animals are injected IP with 1 ml/kg. B.W CCl_4, then after one hour they were injected IP with QTU (125 and 25 mg / kg B.W respectively).

The experiment lasted for 28 days, after that only one male mating was allowed to mate two females. The mating duration lasted for 10 days, when the females are separated in individual cages till the parturition .Once the females rats gave birth, the number of new births were calculated, and the sperm viability and fertility percentage were documented. The results showed a significant reduction ($P<0.05$) in the birth number, sperm viability and fertility percentage in the CCl_4 treated group, The novel compound ameliorates the reduction in birth number sperm viability and fertility percentage that caused by administration of CCl_4 It is concluded that the new derivative of quercetin has an effective antioxidant activity, evident as its capability to inhibit carbon tetrachloride oxidative stress in mature male rats. In addition, the sperm viability parameters and fertility percentage have been improved.

This study overall concluded that this new derivative of quercetin **[Z-1-(-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4 *H* –chromen-4-ylidene) thiourea]** has an effective bioactivity more that in pure quercetin by reducing its cytotoxicity and increasing number of antioxidant activity in chemically building units.