SUMMARY

The present work is concerned with the study of the effect of leflunomide (**LEF**), an anti-rheumatic drug, on the albino mice foetuses of the same strain because the appearance of new anti-rheumatic drugs has raised important questions about foetal safety if a woman becomes pregnant.

The experimental albino mice, were provided from Theodor Bilharz research institute; El Nile road, Warrak El Hadar, Embaba, Egypt. The used mice were arranged in the following groups:

G_1 (C♂+C♀): Males and females were injected daily for 15 days with the dose solvent (1% carboxymethyl cellulose; C.M.C.) then they were allowed to mate with each other.

G_2 (T♂+C♀): Males were treated orally for 15 days with the dose "5mg **LEF**/kg/d". These males were allowed to mate with control females.

G_3 (C♂+T♀): Females were treated orally for 15 days with the dose "5mg **LEF**/kg/d". These females were allowed to mate with control males.

G_4 (T♂+T♀): Males and females were treated orally for 15 days with the dose "5mg **LEF**/kg/d". The treated mice were allowed to mate with each other.

On the 20th day of gestation, mice foetuses were collected to be examined. LEF treatment causes the following effects:

1- Increase the percentage of mortality in mice.

2- Decrease the percentage of mating in females more than males.

3- Decrease the rate values of baby weight in mice.

4- Increase in the percentage of abortion.

5- Decrease in maternal uterine weights.

6- Increase in the percentage of foetal mortality "Resorption and stillbirths".

7- Decrease in lengths and weights of foetuses.

8- No external foetal malformations.

The microscopic examination of the liver tissue of foetuses "on the 20th day of gestation" revealed the histopathological effects of the used dose of **LEF**. These changes included great damage of normal liver architecture and disruption of the lobular arrangement of the liver. Many vacuolar changes were seen in the cytoplasm. Some hepatocytes showed broken cellular membranes. Enlarged kupffer cells and endothelial cells were demonstrated. Dilated blood vessels and hepatic sinusoids were also seen. The dilated and engorged hepatic veins with blood indicated the occurrence of hemorrhage.

Histochemically, a clear reduction in DNA and protein content of the foetal liver of the 2nd and 3rd groups (T♂+C♀ and C♂+T♀) was observed denoting cellular degeneration in the hepatocytes. The histochemical studies revealed also an increase in the DNA and protein content of the foetal liver of the 4th (T♂+T♀) group due to the histopathological changes that occurred in the hepatocytes.

In the present work, the molecular technique "Polymerase chain reaction- restriction fragment length polymorphisms (PCR-RFLPs)" investigated the effect of the drug on the cytochrome oxidase subunit VIII **(COX8)** gene of foetuses. The polymerase chain reaction (PCR) facilitates amplification and analysis of selected fragments or genes of DNA. The selected gene (**COX8**) of foetuses of each group has been amplified using the PCR technique. RFLPs profiles of the selected gene of foetuses of the different groups were obtained by digestion with eleven endonuclease. The restriction fragment length polymorphisms (**RFLPs**) enabled specific identification and genetic differentiation between the different studied groups.

The obtained results confirmed that **LEF** has a mutagenic effect on the selected gene (**COX8**) of the foetuses on the 20th day of gestation. Some of these mutations have been detected using the bioinformatics.

The bioinformatics approach has enabled us to predict the RNA secondary structures transcribed from **COX8** genes of foetuses of the different studied groups. The predicted RNA secondary structure transcribed from **COX8** gene of foetuses of the 4th (T♂+T♀) group is the most stable structure while that of the 3rd (C♂+T♀) group is the least stable one. This approach has also enabled us to study the phylogenetic relationship between foetuses of the different studied groups. The foetuses of the 1st (C♂+C♀), 2nd (T♂+C♀) and 3rd (C♂+T♀) groups are closer to each other than those of the 4th (T♂+T♀) group.