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ORIGINAL ARTICLE

Phytochemical effects of genistein and daidzein on sex hormones and corticosterone in female adult rats exposed to Chlorpyrifos

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Abstract

Objective Chlorpyrifos (CF) residues detected in crops because of its widespread use as insecticide. CF toxicity linked to the oxidative stress and lipid peroxides accumulation. Soy isoflavones, mostly genistein (GS) and daidzein (DZ) are antioxidants. The present research aim was to know the effects of either DZ, GS or their combinations with CF on the reproductive performance of female rats and to investigate whether GN or DZ might have protection against pesticide toxicity.

Methods Healthy adult female albino rats divided into five groups of six rats each. The first group was control received corn oil, second group treated with CF 6.7 mg/kg, third group treated with CF 6.7 mg/kg + GS 21.7 mg/kg, forth group treated with CF 6.7 mg/kg + DZ 17.4 mg/kg and the last group given 6.7 mg/kg CF + 21.7 mg/kg GS + 17.4 mg/kg DZ, all are oral daily doses for six weeks. In the end, rats sacrificed and the blood samples collected for biochemical analysis and ovary tissues collected for histopathology analysis.

Results No deaths or changes in the appearance of animals reported throughout the study period. There was a significant body weight increase in all groups except for CF group. Treatment groups of CF alone or with either GS, DZ or their combination for 42 days show a significant reduction of serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH), in addition to significant increase in serum corticosterone level in female rats. Histopathology results of rat ovaries consistent with the biochemical tests.

Conclusions GS or DZ provides no protective effect against oxidative stress induced by CF. However, GS and DZ together have a synergistic effect producing same effect as oxidative stress induced by CF. further studies required to confirm this synergistic effect and reproductive toxicity in female rats.

Keywords Chlorpyrifos · Genistein · Daidzein · Ovary histopathology · Corticosterone

Introduction

Chlorpyrifos (CF) is one of the most common organophosphorous (OP) insecticides. Because of its widespread use, CF residues have been detected in crops [1, 2] and in air [3] which are considered hazardous to living organisms [4]. CF and in particular chlorpyrifos ethyl, have led to adverse effects including genotoxicity, teratogenicity, and immunotoxicity, in addition to hepatotoxicity, as well as neurochemical and neurobehavioral changes [5, 6].

The mechanism of OP Toxicity is mainly through the inhibition of the enzyme acetylcholinesterase (AChE) that hydrolyse acetylcholine (ACh), this inhibition results in accumulation of ACh in the peripheral and central nervous systems at the cholinergic receptors. However, the toxicity arises at the doses that do not inhibit AChE. Thus, other mechanisms implicated in OP toxicity, such as the oxidative stress induction, leading to free radical generation. Several studies documented the association between the oxidative stress and the toxicity induced by OP [7].

Hypothalamic–pituitary–adrenal activation in the conditions of acute stress causes neuron stimulation in hypothalamus, lead to the release of vasopressin and corticotropin-release hormone that stimulates pituitary gland to release adrenocorticotropic hormone (ACTH), which in

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sequence indorses the release of catecholamines, glucocorticoids and mineralocorticoids from adrenal gland [8]. Exposure to organophosphate enhanced ACTH releases that favour cortisol release [9].

Modern epidemiological studies recognised a relationship between organophosphorous insecticides and reduced reproductive capacity [10, 11]. As organophosphorous, insecticides frequently discovered in food, the effects of low doses of CF on the reproductive system considered in animal studies [7, 12]. Long-time exposure to CF causes a significant reduction of sperms mobility and number, as well as increase in the immobility and the abnormal shaped sperms in rats [12, 13].

Soy isoflavones can bind to estrogen receptors because of their estrogen-like structure. Genestein (GS) and daidzein (DZ) are the main isoflavone phytoestrogens in the soy products. GN and DZ are similar in structure to 17-β-oestradiol and display oestrogenic effects [14]. Then, it increases follicle development by upregulating expression of gonadotropin receptors mRNA after the period of the peak laying [15]. GN and DZ are phytoestrogens with antioxidant and neuroprotective effects and displayed synergistic effects [16–18]. GN and DZ antioxidant activity both in vitro and in vivo and the intake of GN and DZ shown to protect against oxidative modification of the low-density lipoprotein (LDL) in human plasma, some GN and DZ incorporated into LDL particles. Incorporation of esterified GN and DZ increased the resistance of LDL to the copper intermediated oxidation in vitro. Previous study assessed the antioxidant potency of GN (0.32 mg/g) and DZ (0.25 mg/g) using the anti-DPPH free radical assay and the FRAP assay revealed that isoflavone glycosides in the soybean possessed a similar antioxidant potency to the GN and DZ aglycones [19].

GN found naturally in soybeans, chickpeas, lentils, sunflower seeds and other soy products [20]. Studies revealed that GS exposure in rats modifies folliculogenesis in vivo [21, 22]. However, the results have differed depending on the age, sex and the dose. Exposure to 50 mg/ kg of GS reduces the healthy primitive follicles primary and secondary, but in 18 days old rats upsurge the amount of antral follicles, indicating that GS fastens the recruitment of follicles. Moreover, that study revealed that exposure to GS dose of 50 mg/kg raises the number of antral and the atretic secondary follicles indicating that the follicles accelerated by GS may not survive to generate feasible oocytes [21]. Contrariwise, another study on 3 month old rats revealed that exposure to GS dose of 160 mg/kg raises the primordial and reduces the antral follicles, indicating that GS inhibits the follicles growth [22]. In addition, supplementation of isoflavone to quail food in the post-peak of egg production enhances the quality of eggs [23]. GS shown to bind to estrogen receptors [24], with more affinity to ESR2 than ESR1, thus making the ovary, which is an estrogen receptor-rich tissue a major target for GS [25].

DZ is a natural phytoestrogen with estrogenic effect, its activity about 10^{-5} times that of 17β estradiol [25]. DZ is isolated mostly from natural foods, such as cereals, beans, and grasses. Due to DZ estrogenic activity, it can bind directly to the estrogenic receptors and regulate animals hypothalamic/pituitary/ and gonadal alliance of the endocrine system [26]. Previous study on female geese showed that DZ supplement increases fertility and egg weight, in addition to its effect on serum progesterone, growth hormone and thyroxin concentrations [27]. A study reported that DZ supplementation to Shaoxing ducks enhances the production of eggs post-peak in a dose-related manner [28].

In general, much study has focused on the presence of GS, DZ and CF, independently in diet and their effects on the animal's reproductive system. However, data are missing that describe the effect of a mixture of these three compounds in the daily diet on the animal's reproductive system.

Therefore, the main aim of the present research was to determine the effects of a mixture of either DZ or GS or their combination with CF on the reproductive performance of female rats. Furthermore, to investigate whether soy isoflavones such as GN and DZ might have protective effect against pesticide-induced reproductive toxicity.

Results

This study revealed no deaths in all experimental groups throughout the study period and no change in overall appearance of animals reported. Further, rats did not display any seeming signs of toxicity such as lacrimation and tremor. There was a significant body weight increase in all groups except CF group, as shown in Fig. 1.

Exposure to 6.7 mg/kg body weight CF alone or with either GS, DZ or their combination for 42 days results in

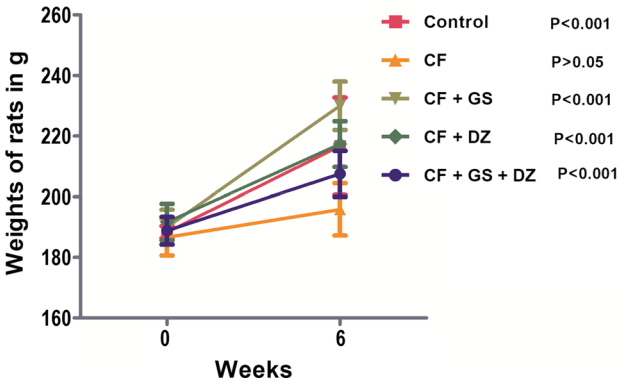

Fig. 1 Differences in the body weight of rats in the studied groups. All data presented as mean ± SEM. Chlorpyrifos (CF), Genestein (GS) and daidzein (DZ). $P < 0.05$ is significant difference

significant reduction of serum luteinizing hormone (LH) and serum follicle-stimulating hormone (FSH) in female rats. While administration of CF alone or in combination with GS and DZ results in significant increase in serum corticosterone level in female rats. Furthermore, administration of CF with GS or DZ found to have no significant effect on serum corticosterone level, as shown in Fig. 2.

Histopathological examination of ovaries

The rat's ovaries of all groups were excised for investigation under the light microscope and the results of control rats administered corn oil only indicated that the ovaries within the normal limit, there are numerous primordial follicles, primary and secondary follicles, Graafian follicles and corpus luteum, as illustrated in (Fig. 3-a). While, the ovary section of rats administered 6.7 mg/kg bw CF in corn oil daily for six weeks showed a degenerative changes in most of the parenchymal tissue with cystic follicles and congestion as well lysed oocyte of follicle, as presented in (Fig. 3-b).

Ovaries from rats treated with a daily dose of CF (6.7 mg/kg bw) and GS (21.7 mg/kg bw) for six weeks showed follicles with lysed oocytes and epithelial lining of follicles with no indication of ovulatory process, necrosis was found in massive area of the parenchymal tissue with congestion, as presented in (Fig. 3-c). While the ovary section of rats treated with a daily dose of CF (6.7 mg/kg bw) and DZ (17.4 mg/kg bw) for six weeks showed lysed follicles with cystic ovary, atreatic primary and secondary follicles with massive degeneration, haemorrhage, and corpus luteum, as illustrated in (Fig. 3- d). The ovaries of rats treated with a daily dose of CF (6.7 mg/kg bw) + GS (21.7 mg/kg bw) + DZ (17.4 mg/kg bw) for six weeks, show follicular cyst, with multi post ovulatory corpora lutea and newly ovulatory corpora lutea (Fig. 3- e).

Discussion

Organophosphorus pesticides are the main pesticides used in agriculture, their wide use have a deep influence on the environment, dangerous effects on human and all other organisms and it is easily find their way to human by the food chain in addition to the direct effect from air and dust that contain many contaminants including plant fragments [29, 30]. Wide use of these pesticides causes continuous exposure to low doses that can cause a variety of metabolic, fertility, cardiovascular, psychiatric and other hormonal diseases [31].

The results revealed a significant body weight increase in all groups except for CF group showing a significant

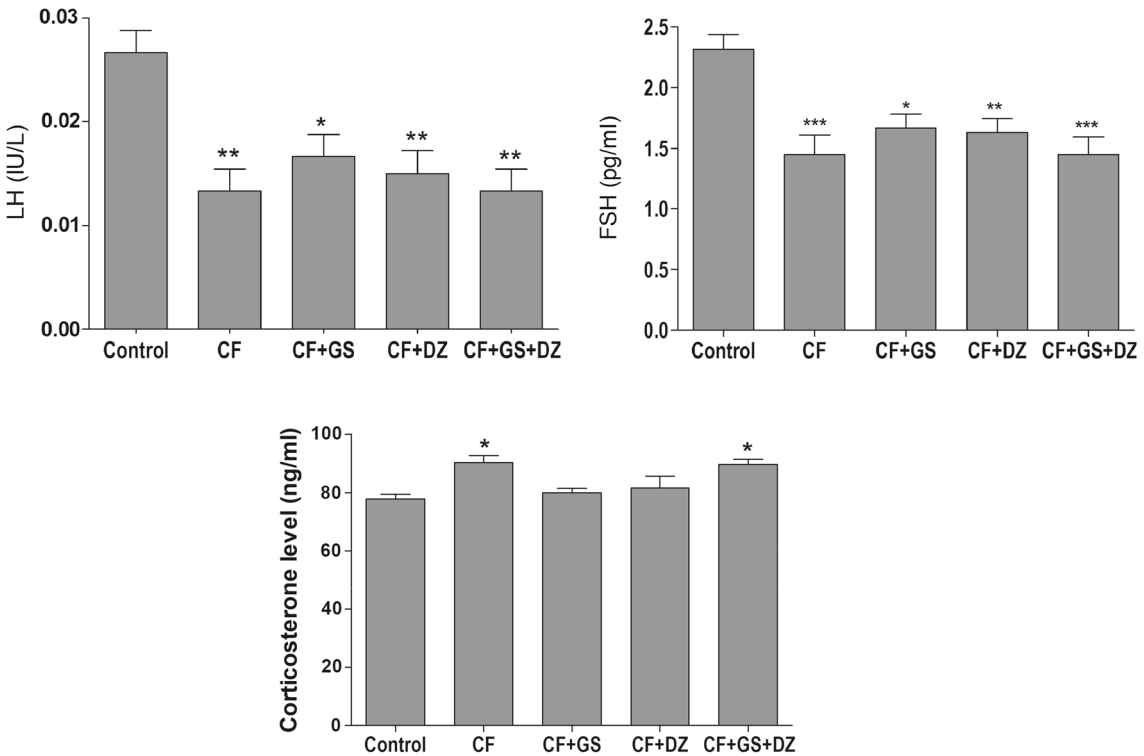

Fig. 2 Effect of 6.7 mg/kg bw chlorpyrifos (CF), 21.7 mg/kg bw Genestein (GS), 17.4 mg/kg bw daidzein (DZ) and their CF combinations on serum luteinizing hormone (LH), follicle stimulating hormone (FSH) and corticosterone levels in different studied groups. All data presented as mean ± SEM. (***$p < 0.0001$, **$p < 0.001$ and *$p < 0.05$) in comparison to control

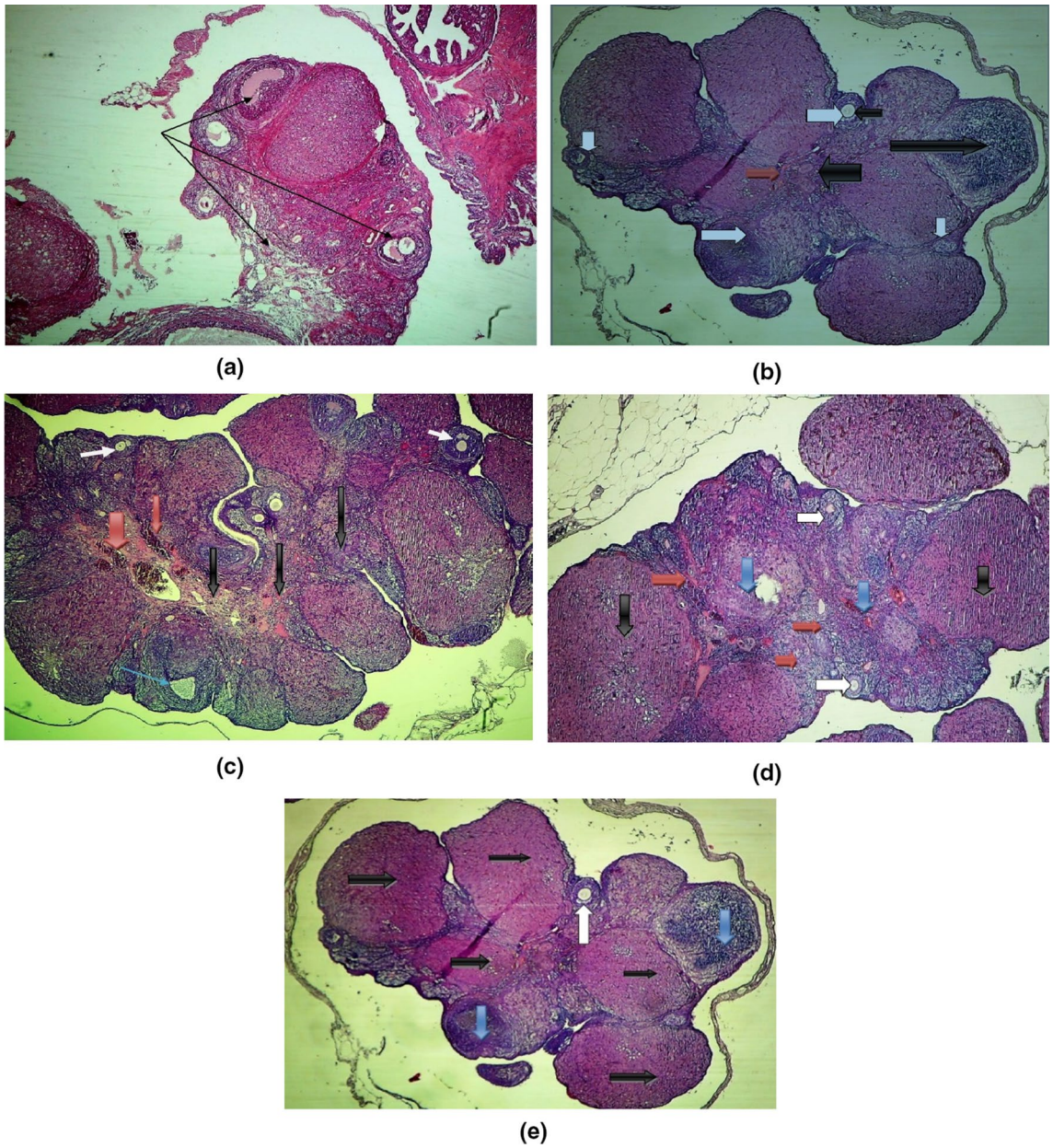

Fig. 3 Light micrographic section of female rat ovary (stained with H and E) 200X. **a** Control: shows normal follicle growth (thin arrow) **b** CF: shows lyses of oocyte (thick arrow), degenerative changes in parenchymal tissue with cystic follicles (black arrow) and congestion (red arrow). **c** CF and GS: shows follicles lyses of oocytes (white arrow), with cystic follicles (blue arrow), necrosis was found in massive area of the parenchymal tissue (black arrow) with congestion (red arrow). **d** CF and DZ: shows follicles lyses with cystic ovary (white arrow), atreatic primary and secondary follicles (red arrow) with massive degeneration and hemorrhage (blue arrow), and corpus luteum (black arrow). **e** CF, GS and DZ: shows follicular cyst (white arrow), with multi postovulatory corpora lutea (black arrow) and newly ovulatory corpora lutea (blue arrow) 1.

decrease in body weight gain and this reduction in body weight gain could be related to oxidative stress [32]. Soybean is one of the large crops and a vital raw material for manufacturing edible oil [33]. GN and DZ are phytoestrogens with antioxidant and neuroprotective effects and displayed synergistic effects [16–18]. The results revealed a significant body weight increase in all rats administered soy isoflavones and these data consistent with fat Zucker rats, which presented that high level of soy isoflavones, augmented weight gain in female rats but did not affect visceral fat [34].

The results exposed that administration of CF to female rats caused significant reduction in serum LH and FSH levels, and these results consistent with other studies showed

that pesticides such as CF act like antagonists to androgen receptors of gene expression related to hypothalamic gonadotropin synthesis or steroidogenesis [35, 36]. The results exposed that administration of GS, DZ, or both with CF to female rats caused significant reduction in serum LH and FSH levels, indicating that soy isoflavones have no protective effect against CF-induced reduction in these hormones. Furthermore, histopathology results of rat ovaries consistent with the biochemical tests.

Most studies on phytoestrogens focused on reproductive steroids, very little known about phytoestrogens effect on glucocorticoids. In vertebrates, glucocorticoids, for example, cortisol regulates the reproduction and considered as a critical factor in a response to stress [37]. Organophosphate exposure causes increase in acetylcholine levels favour the cortisol release secondary to enhanced secretion of ACTH [9]. In this study, CF group showed a significant rise in corticosterone levels compared to the control group, these results are in cope with previous study in rats [38].

To our knowledge, much study has focused on the presence of GS, DZ and CF, independently in diet and their effects on the animal's reproductive system. However, data are missing that describe the effect of a mixture of these three compounds in the daily diet on the animal's reproductive system.

Materials and Methods

Materials

CF 48% TC (Al-Ardh Attyiba Co. for Manufacturing of Vet & Disinfectants, Amman—Jordan), diluted in corn oil to get a final concentration of 10% emulsion. GS (5,7- dihydroxy-8-[4-hydroxyphenyl]chromen-4-one) and DZ (4,7 Dihydroxyisoflavone) powders both from axenic research and formulation materials, China. GS and DZ dissolved in distilled water.

Methods

Thirty adult Sprague–Dawley female rats with (weights of 170–200 gm) were involved in this experiment. The rats purchased from Hella University/ College of Science and acclimated for a period of one week before starting experiment. Every three animals caged in a plastic cage with standard bedding. Experiments of this study performed according to the National Institute of Health (86/609/EEC) Guidelines for using Laboratory Animals.

Furthermore, College of Pharmacy /University of Basrah / Ethical Committee approval number 3/5/115, September 2020 obtained. The animals hosted in groups under suitable situations at room temperature of 25 ± 3 °C and humidity, with regular rhythm 12 h Light and 12 h dark. Animals served a pellet diet without soy and the drinking water supplied all the time.

Experiment

Thirty adult female albino rats equally divided into five groups of six rats each. Animal weights measured at the beginning and at the end of experiment. Group 1 rats represent the control group, administered corn oil (1 ml /kg body weight)/ day orally by gavages. Group 2 rats administered orally CF 1/20th LD50 (6.7 mg/kg bw)/ day dissolved in 1 ml corn oil by gavages. Group 3 rats administered (6.7 mg/kg bw CF + 21.7 mg/kg bw GS) daily. Group 4 rats administered (6.7 mg/kg bw CF + 17.4 mg/kg bw DZ) daily. Group 5 rats administered (6.7 mg/kg bw CF + 21.7 mg/kg bw GS + 17.4 mg/kg bw DZ) daily Doses were selected according to the previous researches.

After six weeks, the end of experiment period, the overnight fasted rats were sacrificed and then the blood samples were taken by intracardiac puncture and the sera collected by centrifugation at 855 × g for 10 min. Sera were kept for biochemical tests at – 200 °C.

The heart from each rat removed and washed with saline solution (0.9%), then separated longitudinally into two parts and fixed in 10% formalin for histopathological examination.

Biochemical analysis

Serum level of luteinizing hormone (LH) and follicle stimulating hormone (FSH) measured using Abbott architect i1000SR (Abbott Diagnostics, Chicago, USA) as per the manufacturer's instructions.

Histopathological investigation

Histopathological investigation was prepared by fixing the tissues in 10% solution of formalin for about 4 days, after that the tissues prepared as sections, and covered with paraffin. The size of cut of histological pieces is 4 to 5 µm, stained by routine hematoxylin (H) and eosin (E) stains. After staining, the sections were examined under a light dissection microscope.

Statistical analysis

Statistics achieved using Graph Pad Prism software (version 7.0, Inc., San Diego, CA). Descriptive data presented statistically as mean ± SEM for wholly estimated parameters. One-way analysis of variance (ANOVA) and Tuckey's Multiple Comparison tests used for comparison between groups. p values less than 0.05 considered as significantly different.

Conclusion

GS or DZ provides no protective effect against oxidative stress induced by CF. However, GS and DZ together have a synergistic effect producing same effect as oxidative stress induced by CF, further studies required to confirm this synergistic effect and reproductive toxicity in female rats. Furthermore, significant body weights increase in all rats administered soy isoflavones compared to CF alone.

Suggestions for future work

1. Evaluating the Combination Index or synergistic index to measure synergism of GS and DZ effects.
2. Finding the molecular mechanisms behind this synergistic effect of GS and DZ.
3. Further studies required to check Kisspeptin gene mRNA levels, which are, involve reproduction regarding GS and DZ treatment.

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Declarations

Conflicts of interest Shigaf Daham Abdulretha, Asia Selman Abdullah and Muhsin S.G. AL-Mozie'l declare that they have no conflicts of interest.

Ethical approval All tests performed in agreement with the National Institute of Health Guidelines for the Treatment and Use of Laboratory Animals (86/609/EEC) and permitted by Basrah University, College of Pharmacy Ethical Committee.

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