Introduction

Contraception plays a major role in managing women′s reproductive health **(Medical Research Council, 2003).** There are different contraceptive methods that can be used, which include hormonal and natural methods **(Farrer, 2009).**

Combined oral contraceptives are a well-established method of contraception with proven efficacy and have been available for over 40 years **(Rosenberge et al., 1999).** Since their introduction, however, oral contraceptives have undergone extensive study, continual development, and significant improvements. Unlike the original oral contraceptives, new low-dose oral contraceptives have few health risks when used by properly selected women and many health benefits **(Blackburn et al., 2000).** Use of this contraceptive by young women, however, has been associated with a number of adverse effects and contributes to nutrient deficiencies, such as loss of bone mineral density **(Kaunitz et al., 2006)**, decrease serum phosphorus and magnesium in (OC) users **(Akinloye et al., 2011 and Dante, 2014).**OCs further possibility of iron deficiency anemia **(Veninga, 1984)**. Several studies have found low mean serum vitamin B12 levels in women using OCs **(Thane et al., 2002**) and reduced folate storage in the body and resulted in megaloblastic changes in cervical epithelium (**Li, et al., 1995)**. Oral contraceptive in some cases has been linked to obesity and hypercholesterolemia **(Obisesan et al., 2002).** Long-term use of oral contraceptives during reproductive age may be a risk factor for developing diabetes after menopause (**Kim et al.,2016) and**Glaucoma(**Wang et al., 2016).**

Taking dark leafy vegetables represented by watercress rich in antioxidants (**Santos et al., 2014)**, minerals and vitamins (**Rose et al., 2000)** may reduce the side effects of taking oral contraceptives.

Watercress *(Nasturtium officinale)* is a valuable source of vitamins and a good detoxifying herb. This plant contains a relatively large amount of vitamins B1, B2, C and pro-vitamin A, folic acid, glucosinolates, iodine, iron, protein, and especially calcium and sulphur compounds, which influence its characteristic odor, but also adds to its nutritional benefits **(Palaniswamyet al., 2003).**

Watercress leaves are traditionally used as a stomachic, depurative, diuretic, expectorant, hypoglycemic, odontalgic and

stimulant **(Bahramikia et al., 2008**), It also cures pain, ulcers, jaundice and fever. Meanwhile, it has been used to treat asthma, bronchitis, scurvy, tuberculosis and urinary tract infection and calculi **(Zaragari, 2011).** Theplant possesses antimicrobial, antioxidant **(Ozen, 2009),** antiestrogenic**,** anticarcinogenic activities **(Tamayo, 2000).** It is also considered as an excellent functional food for the prevention of cancer **(Potter, 1996).**

This study was conducted to investigate the effectiveness of administration different types of oral contraceptives pills on concentration of some vitamins, minerals, liver functions and lipid profile on adult female rats. At the same time, the protective effect of watercress supplementation on compensation the deficiency of minerals and vitamins concentration was studied.

Materials and Methods

Materials:-

Chemicals and OCs pills: Casein, vitamins, minerals and cellulose were purchased from El-GomhoriaCompany – Cairo – Egypt. Oral contraceptive pills were obtained from Ministry of Health contains (0.15mg ievonorgestrel and 0.03 mg ethinyle esteradol), and other commercial pills that contains (3 mg of drospirenone and 0.03 mg of ethinyl estradiol) produced by Bayer Pharma, Germany, purchased from local Pharmacy. Kits for blood analysis were purchased from Gama Trade Company for Chemical, Cairo, Egypt.

Rats: Adult female albino rats (Sprague- Dawley strain) (n=30 rat) weighing approximately (200±5 g.) were purchased from Helwan Experimental Animals Station.

Plants: Watercress was purchased from local market**.**

Methods:

Preparation of OCs solution: Twenty-one (21) tablets of each drug were dissolved in 100 ml of distilled water, 0.6 ml/kg of the drug was given by oral gavage for every four days with one day break for eight weeksaccording**(Toryila et al., 2014)**.

Preparation of dried watercress: Watercress was cleaned, washed, dried by solar energy at the National Research Center, Dokki, Egypt and well grinded to get the fine powder. Watercress added to basal diet at 10%.

Experimental Design: This study was carried out at the animal house of Home Economics Faculty, Helwan University. Thirty female albino rats were housed in well aerated cages under hygienic conditions and were fed on basal diet for one weekfor adaptation.After this week rats were divided into five groups (6 rats each) as follows: - The first group was fed on basal diet and served as a control negative group. The second and third group were fed on basal diet and given orally OCs of Ministry of Health (OCMH) or OCs from local Pharmacy (OCLP) at the dose of (0.6 ml/kg BW) respectively. The fourth and fifth groups were fed on basal diet supplemented with 10% dried watercress and given orally (0.6 ml /kg BW) of OCMH or OCLPrespectively.

At the end of the experimental period (8 weeks), rats were fasted overnight before sacrificing and the blood samples were collected from each rat then centrifuged for 15 min at 3000 rpm to separate the serum. Serum samples were carefully separated into dry clean wasserman tubes using a Pasteur pipette and kept frozen at -20^{o}C until analysis.

Chemical analysis: Serum calcium, phosphorus, magnesium, iron, vitamin B12 and folic acid were measured according to the method of (**Zake et al, 1975, Youngs, 1990, Bauer, 1984, Thomas, 1998, Luox, 2006, Kalmbach et al, 2011)** respectively.Serum total cholesterol **(Richmond, 1973),** triglycerides **(Wahlefeld, 1974),** high density lipoprotein (HDL-c) **(Albers et al., 1983)** were determined**.** Meanwhile, low density lipoprotein (LDL-c) and very low density lipoprotein (VLDL-c) were calculated according to **(Fridewald et al., 1972).**Activities of liver enzymes; alanine and aspartate amino transferases (ALT & AST), were determined according to the method of **(Bergmeyer et al., 1978).**

Statistical Analysis: -The obtained results were analyzed according to SPSS program version 18. ANOVA test was used to compare results among groups**,** P-value of <0.05 was considered statistically significant**(SPSS, 1986).**

Results and discussion:

The obtained results in Table (1) indicated that rats given orally OCMH or OCLPhad significant decrease (P<0.05) in serum calcium, phosphorus, iron and magnesium compared to control group.

According to the study by **(Singh et al., 1985)**, the calcium uptake was decreased after 30 and 90 days of treatment of steroidal oral contraceptive, comprising megestrol acetate (5 mg/kg body weight) plus ethinyl estradiol (0.05 mg/kg body weight).**Hameed et al., (2011)** showed that, there was significant decrease in serum levels of calcium, in women taking oral contraceptives. Other studies showed that OC use is associated with decreased bone mineral denesity of the spine and the femoral neck in female endurance athletes, and that early age at initiation of OC use may be an important risk factor for low peak bone mass in young women **(Hartard et al., 2004;Shope and Snow, 2005 and Scholes, 2001)**.Moreover, the current results were in the line with **(Hameed et al., 2001; Akinloye et al., 2011 and Dante, 2014)** whom mentioned a decrease in the serum concentrations of phosphorus and magnesium in OC users. OCs further influence serum B12 concentrations and the possibility of iron deficiency anemia **(Veninga,1984).Li, et al., (1995)** reported that, oral contraceptives reduced folate storage in the body and resulted in megaloblastic changes in cervical epithelium. This condition was improved with folic acid therapy.

On the other hand addition with watercress at 10% to rats that fed on basal diet and given orally oral OCMHor OCLP caused significant increase ($P<0.05$) in the mean value of serum calcium, phosphorus, iron and magnesium compared with rats given OCMH or OCLP only. It was also observed that OCMHcaused the most harmful effect on the level of calcium, phosphorus, iron and magnesium. It was recommended thatdairy product intake necessary to achieve the recommended intakes of calcium, protected the total hip BMD and spine BMD from loss observed in young healthy women with low calcium intakes who were using OC **(Teegarden et al., 2005).**

In regarding to the effect of OCs on vitamin status, results in Table (2) illustrated that, rats given orally OCMH or OCLPhad significant decrease ($P<0.05$) in serum folic acid and vitamin B12. While addition with 10% dried watercress to rats that fed on basal diet and given orally OCMH or OCLPcaused significant increase ($P<0.05$) in the mean value of serum folic acid and vitamin B12 compared with rats given OCMH or OCLP only.

Several studies have found low mean serum vitamin B12 levels in women using OCs as compared to non users **(Thane et al., 2002; Lussana et al., 2003 andBerenson and Rahman, 2012),** the

levels of transcobalamin I, a glycoprotein serves to protect vitamin B12 from acid degradation in the stomach, were also lower in OC users**(Shojania, 1982).**Folate status was significantly lower among oral contraceptive users**(Shere et al., 2015).**OCs are available which contain metafolin (calcium salt of L-5-methyltetrahydrofolate; Metafolin®). (**Holzgreveet al., 2012).** Previous studies have suggested that it is the metabolism, and not the absorption, of folate and vitamin B12 which is affected by OC use**(Jaffar et al., 1983).**Evidence of vitamin B6 deficiency has been found among combination OC users in numerous studies. Derangement of tryptophan metabolism occurs within 1 month of initiation of OC use. OCs also may cause a deficiency of pyridoxal phosphate, a coenzyme needed for the tryptophan-nicotinic acid pathway. It is recommended that OC users take 1-1.5 mg/day of supplemental vitamin B6; new OC users should take 5 mg/day until plasma levels of 1.5-2 mg have been achieved**(Veninga, 1984).**

Table (3) showed that rats given orally OCMH or OCLP had significance increase ($P<0.05$) in serum TG, LDL-c and VLDL-c, whilethe level of HDL-c was significantly ($P<0.05$) decreased compared to control group. The mean level of serum TC didn't change among the rats given OCMH or OCLP compared to control group. On the other hand, supplementation with 10% watercress significantly lowered lipid profile (TC,TG, VLDL-c and LDL-c) and increased HDL-c compared to control group.

Use of very low dose OC containing desogestrel can elevate lipid levels **(Berenson et al., 2009)**. **Yesmin et al., (2013)** reported that OCs increase apolipoprotein B- synthesis and thus increased TG and LDL. Higher LDL-c in oral contraceptives users' women might be due to increase lipoprotein synthesis rather than impaired lipolytic catabolism, in association with accumulation of cholesterol as a result increased LDL. Increased serum TG might be due to increase production and transport of VLDL that endogenously synthesized triglycerides in the blood. Progestin components of oral pill increased hepatic lipase enzyme activity as a result decreased serum HDL level. Protein and phospholipids component of LDL are susceptible to oxidized in long term contraceptives users' women. Oxidized LDL can damage the arterial endothelium and is more likely to accumulate in the arterial intima, thus contributing to endothelial damage.

Kern and Everson (1987) showed that contraceptive steroids increase the risk of acquiring cholesterol gallstones. The factors responsible include an increase in cholesterol saturation of bile and an increase in rate of secretion of cholesterol into bile. The combination of ethinylestradiol and drospirenone induced the heightening of lipid peroxidation correlated with high levels of copper, a situation that could be associated with increased cardiovascular risk **(De Groote et al., 2009).**

The effect of oral contraceptives on liver functions of female rats was illustrated in in Table (4).OCMH or OCLPcaused a significant increase ($P<0.05$) in serum AST and ALT compared to control group. While addition with dried watercress at 10% to rats that fed on basal diet and given orally oral contraceptive OCMHor OCLPlowered the elevated liver functions compared to other groups

The introduced combination of ethinylestradiol and drospirenone induced the heightening of lipid peroxidation correlated with high levels of copper, a situation that could be associated with increased cardiovascular risk **(De Groote et al., 2009).**

Conclusion: Nutritional counseling is particularly needed by OC users, who may be deficient in one or more of the essential vitamins or minerals. Nutritional counseling should be an ongoing part of any comprehensive patient-teaching program

Table (1): Effect of oral contraceptive pills on some minerals in female rats.

Parameters / Groups	Calcium mg/dl	Phosphorus mg/dl	Iron µmol/L	Magnesium (mg/dl)
Group (1) : Control	13.50±0.17 [a]	5.30±0.43 [a]	269.60±1.63 [a]	2.06±0.06 [a]
Group(2): OCMH	8.84±0.27 [d]	2.97±0.03 [c]	214.60±4.15 [d]	0.76±0.10 [d]
Group (3): OCLP	10.08±0.25 [c]	3.16±0.11 [c]	230.40±6.61 [c]	1.10±0.16 [c]
Group(4): OCMH**+Watercress (10%)**	11.70±0.64 [b]	3.94±0.20 [b]	241.80±4.89 [c]	1.48±0.04 [b]
Group (5): OCLP **+Watercress (10%)**	12.16±0.38 [b]	4.25±0.30 [b]	256.00±1.73 [b]	1.63±0.06 [b]

Values are expressed as mean ± SE.

Values at the same column with different letters are significantly different at $P < 0.05$.

Table (2) Effect of oral contraceptive pills on B- complex vitamins in female rats.

Parameters / Groups	Vitamin B12 µg/dl	Folic Acid µg/dl
Group (1) :Control	2.78±0.21[a]	3.24±0.11[a]
Group(2): OCMH	0.81±0.18[c]	2.02±0.02[c]
Group (3): OCLP	0.85±0.13[c]	1.98±0.01[c]
Group (4): OCMH **+Watercress (10%)**	1.76±0.09[b]	2.61±0.15[b]
Group (5): OCLP **+Watercress (10%)**	1.91±0.7[b]	2.62±0.14[b]

Values are expressed as men ± SE .
Values at the same column with different letters are significantly different at $p < 0.05$.

Table (3): Effect of oral contraceptive pills on lipid profile in female rats.

Parameters / Groups	Cholesterol	Triglycerides	HDL-C	LDL-C	VLDL-C
	mg/dl				
Group (1) :Control	91.20 ± 2.31[a]	98.80± 2.47[c]	66.60 ± 1.98[a]	4.84 ± 1.17[b]	19.76 ± 0.49[c]
Group(2): OCMH	93.60 ± 2.01[a]	135.80±1.56[a]	38.20 ± 1.82[c]	28.24 ± 2.29[a]	27.16 ± 0.31[a]
Group (3): OCLP	91.20 ± 3.54[a]	131.80±2.22[a]	41.60 ± 1.69[c]	23.24 ± 3.04[a]	26.36 ± 0.44[a]
Group (4): OCMH**+Watercress (10%)**	80.80 ± 2.51[b]	121.80±2.47[b]	49.60 ± 2.67[b]	6.84 ± 1.12[b]	24.36 ± 0.49[b]
Group (5): OCLP **+Watercress (10%)**	79.20 ± 3.33[b]	115.60±2.94[b]	53.20 ± 2.81[b]	2.88 ± 0.77[b]	23.12 ± 0.58[b]

Values are expressed as men ± SE .
Values at the same column with different letters are significantly different at $p < 0.05$

Table (4): Effect of oral contraceptive pills on liver function in female rats .

Parameters / Groups	ALT	AST
	(µ /L)	
Group (1) :Control	28.80 ± 0.86 [c]	116.80 ± 2.63 [b]
Group(2): OCMH	45.20 ± 4.18 [a]	130.20 ± 2.24 [a]
Group (3): OCLP	45.60 ± 3.23 [a]	128.40 ± 1.20 [a]
Group (4): OCMH+**Watercress (10%)**	37.40 ± 0.50 [b]	119.80 ± 1.15 [b]
Group (5): OCLP **+Watercress (10%)**	36.20 ± 1.31 [b]	122.20 ± 1.15 [b]

Values are expressed as men ± SE .
Values at the same column with different letters are significantly different at $p < 0.05$.

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