RESEARCH ARTICLE

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GENOTOXIC AND MOLECULAR STUDIES ON CYCLOSPORINE A- AZITHROMYCINE INTERACTION AND THE PROTECTIVE EFFECT OF GARLIC DURING ADMINISTRATION

ABSTRACT:
The experiment was conducted to study the effects of both Cyclosporine A- (CsA) and Azithromycine (AZM), and to demonstrate the interaction of combination of CsA with AZM and the protective properties of garlic against each drug of them, besides Cyclosporine - Azithromycine interaction. The study was planned to clarify changes in chromosomal aberrations (CsA), expression of tumor necrosis factor alpha (TNF-α) and biochemical changes in different organs of Male Sprague-Dawley rats during period of oral administration of drug or drugs. The alterations after oral administration of animals with doses equal to 25 mg/kg of CsA, 500 mg/kg of AZM and 300 mg/kg of garlic were estimated after one and seven days. Non significant changes were observed in all types of structural and numerical chromosomal aberrations after one day of oral administration of the used drugs. After seven days of oral administration of CsA alone, CsA + garlic, CsA + AZM, and CsA + AZM + garlic, a significant increase in structural and numerical chromosomal aberrations were noticed. No significant changes in structural and numerical CAs were noticed after seven days of oral administration of AZM or AZM + garlic. The mean values of TNF-α gene expression, when measured with real time PCR assay, revealed that its expression in the three control groups were higher than the groups received the drug alone, in case of AZM and AZM+ CSA, while the group received CSA alone was the lowest group in TNF-α expression. Biochemical results showed significant changes in serum AST, ALT, GGT, LDH, ALP, globulin, BUN, creatinine and glucose after oral administration of CsA. In conclusion, CsA was genotoxic on chromosomes and TNF-α gene, AZM administration alone or with CsA showed safety protection and minimal interaction while garlic may improve the hazard effect of CsA.

KEY WORDS:
Cyclosporine A, Azithromycine, Garlic, Genotoxicity, TNF-α expression, Biochemical changes

INTRODUCTION:
Drug-Drug interactions (DDI) are important cause of drug related health problems and this includes significant morbidity and mortality. DDI can lead to a variety of adverse events, and it has been suggested that preventable adverse events are the eighth cause of death among patients (Goldstein et al., 2005).

Cyclosporine A (CsA) is a frequently used immunosuppressive agent in transplant medicine to prevent graft rejection (Mascarell and Truffa-Bachi, 2003; Hagar, 2004; Zhang et al., 2007). In addition, it was used in the treatment of wide spectrum of autoimmune diseases such as psoriasis (Hesselink et al., 2004; Kurus et al., 2008), rheumatoid arthritis, inflammatory bowel disease, and asthma (Andrés et al., 2005). CsA is usually administered orally or intravenously (i.v.). Oral preparations may contain corn, castor, or
olive oil in ethanol while i.v. preparations contain 33% ethanol and castor oil vehicle (Corcoran, 2006). The clinical use of CsA presents inconvenient adverse side effects such as hepatotoxicity and nephrotoxicity (Andrés et al., 2001). CsA primary mode of immunosuppressive action appears to be the regulation of T cell function by inhibiting the expression of cytokines such as IL-2 and affects of the expression of TNF-α (Ciesielski et al., 1997; Leitner et al., 2011). In rats treated with CsA, TNF-α levels were lower than in rats received no preventative treatment with a mechanism linking CsA with the prevention of cell death in addition to inhibition of T cell proliferation (Burke et al., 1994; Ciesielski et al., 1997). It is well documented that TNF-α mRNA gene transcription is blocked by CsA (McCaffrey et al., 1994). This drug is extensively metabolized in the liver by CYP3A enzymes (Mehvar and Chimalakonda, 2004). Pharmacokinetics of CsA is characterized by a low clearance and a high volume of distribution in rat tissues (Tanaka et al., 2000).

Azithromycin (AZM) is the first clinically developed antibiotic in a new subclass of the macrolides. It is composed of 15-cyclic lactone antibiotic and semisynthetic erythromycin derivative (Van Bambeke, 1996). It exhibits some advantages over erythromycin including better oral bioavailability, higher tissue concentrations, and fewer side effects. AZM is active against some Gram-positive and Gram-negative and can increase nitric oxide production (Morihara et al., 2002). Because of these beneficial effects of garlic, treatment with garlic extracts was found to improve the activation of natural killer cells, the function of T-lymphocytes and the level of interleukin – 2 (Sumiyoshi, 1997).

The aim of the present study was planned to evaluate the effects of Cyclosporine A, Azithromycine, as well to demonstrate the interaction between both drugs on chromosomes, TNF-α gene expression and on organs functions of rats taking in consideration the protective actions of garlic against the effects of each drug alone or on the interaction of effects between both drugs in combination.

MATERIAL AND METHODS:
Experimental Animals:
A total of 170 Male Sprague Dawley rats (Rattus norvegicus), approximately 2 months old, weighing 70-100 g were obtained from Egyptian Institution of Serum and Vaccine (Helwan, Cairo, Egypt). The rats were housed in specially designed cages and kept in the laboratory under the normal light-dark rhythm, food and water supplement for at least one week before the start of the experiment.

Animal Groups:
Nine groups composed of 10 rat per each were used. Group one animals were kept without medication while the second group received only the vehicle olive oil (2.5 ml), the third group received CsA, fourth group received AZM, fifth group received garlic, sixth group received both CsA and AZM, seventh group received CsA and garlic, eighth group received AZM and garlic, while finally group nine received CsA, AZM and garlic.

Drugs:
CsA, AZM and garlic were administrated for one and seven days by oral route in a dose equivalent to 25 mg/kg body weight in olive oil, 500mg/kg body weight in double distilled water or 300 mg/kg body weight in distilled water, respectively.

Biochemical studies:
Blood samples were collected at the end of experiments. Sera from all samples were separated for measurement of glucose, total proteins, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), aspartate aminotransferase (ALT), gama glutamyl transferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and albumin, by kits supplied by Stainbio Laboratory, Taxas, USA.

Chromosomal analysis:
Five animals of each group were sacrificed after one day of the treatment and
another five animals in the same group were sacrificed after seven days of the treatment by head decapitation at the appropriate sampling time, Colchicine was given at the dose of 1 mg/kg BW i.p. two hours before sacrifice. Chromosomal preparations for scoring both structural and numerical aberrations from bone marrow cells of rat were made according to the method described by (Helbig et al., 1995) with some modifications. Slides were stained with Giemsa and well spread metaphases were analyzed for chromosomal aberrations. Fifty metaphase spreads per animal were examined microscopically for chromosomal aberrations. Only cells with well spread chromosomes were selected for scoring. The mitotic index (MI) is determined as the number of dividing cells in 1000 cells.

RNA Isolation and Real-Time Quantitative RT-PCR:
Using guanidinium thiocyanate-phenol-chloroform extraction method (Stratagene, Germany), to obtain total RNA was isolated from 5×10^3 cell obtained from each tested group. Synthesis of cDNA depended on total extracted RNA using a reverse transcription was performed with random hexamers (Applied Biosystems, USA), MULV reverse transcriptase (Promega, USA), dNTPs (Promega, USA) and 1µl RNase inhibitors (Promega, USA), at 42°C for 50 min, followed by denaturation at 99°C for 5 min. Addition of 1 µL RNase inhibitor (all from Invitrogen-Life Technologies) for another 20 minutes at 37°C. Quantitative real-time PCR was performed on a sequence-detection system (LightCycler 480 II; Roche, Switzerland) using heat-activated Taq DNA polymerase (LightCycler 480 SYBR Green I Master), according to the manufacturer's protocol. Primers were directed to study TNFα (TNF-α sense, 5'-AGAACT CAGGCGGTGTC-3', TNF-α antisense, 3'-GATTCTCTGGGAGCTCCT-5' (484 bp). Endogenous control for expression was based on using β-actin (β-actin sense, 5'-AAG CCT AAG GCCAACCTGAAAG-3' β-actin antisense, 3'-ATACACGGGATCTGAAGCTCG-5' (540 bp). Cycling conditions were as follows: 95°C for 10 min, followed by 40 cycles of 95°C for 5 s and 60°C for 1 min. The amplified mRNA was presented as relative quantities measured by n-fold increase of the amplification treated groups compared to control group. Amplification of β actin mRNA was used as a positive control to estimate the efficiency of the experimental conditions.

Statistical Analysis:
Statistical analysis was carried out by using one way analysis of variance (ANOVA) followed by Post hoc test (Dunkan) using the Statistical Package for the Social Sciences (SPSS) version 10. Histograms of cytogenetic data were drawn using Excel 2007 (Microsoft, USA).

RESULTS:
Chromosomal aberrations (CAs) assay:
Structural chromosomal aberrations observed in the present study were in the form of ring chromosome (Fig.1), and centromeric attenuations (Fig. 2). Numerical chromosomal aberrations were observed in the form of endomitosis (Fig. 3) and polyploidy (Fig.4).
CAs assay after one day of oral administration:

Oral administration of either garlic or olive oil alone to normal rats induced non significant changes in the mean values of all observed types of structural and numerical chromosomal aberrations when compared to that of the normal control group. Similarly, the results of group 3 received CsA alone and group 7 received CsA plus garlic showed non significant change in the mean values of all types of structural and numerical CAs when compared to normal control (group 1), vehicle control (olive oil) (group 2) and garlic (group 5) only (Table 1; Figs 5 & 6).

Table 1. Chromosomal aberrations induced in rat bone marrow cells after one day and seven days of oral administration of different treatments alone or combined.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number of structural chromosomal aberration</th>
<th>Number of numerical chromosomal aberration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Centromeric alteration</td>
<td>Ring chromosomes</td>
</tr>
<tr>
<td>One day</td>
<td>Seven days</td>
<td>One day</td>
</tr>
<tr>
<td>Control</td>
<td>1.2 ± 0.447</td>
<td>1.6 ± 0.447</td>
</tr>
<tr>
<td>Olive oil</td>
<td>1.4 ± 0.548</td>
<td>1.2 ± 0.836</td>
</tr>
<tr>
<td>CsA</td>
<td>1.4 ± 0.447</td>
<td>2.4 ± 0.707</td>
</tr>
<tr>
<td>AZM</td>
<td>0.8 ± 0.448</td>
<td>1 ± 0</td>
</tr>
<tr>
<td>Garlic</td>
<td>1.2 ± 0.837</td>
<td>1.2 ± 0.447</td>
</tr>
<tr>
<td>CsA + ZMA</td>
<td>1.2 ± 0.837</td>
<td>2.2 ± 0.548</td>
</tr>
<tr>
<td>CsA + Garlic</td>
<td>1.6 ± 0.548</td>
<td>2.6 ± 0.894</td>
</tr>
<tr>
<td>AZM + Garlic</td>
<td>1 ± 0</td>
<td>1 ± 0.707</td>
</tr>
<tr>
<td>CsA + AZM + Garlic</td>
<td>1.2 ± 0.447</td>
<td>2 ± 0.548</td>
</tr>
</tbody>
</table>

• Data were expressed as Mean± Standard Deviation (M±SD).
  a: Significant change at P<0.05 with respect to normal control group.
  b: Significant change at P<0.05 with respect to vehicle control (olive oil) group.
  c: Significant change at P<0.05 with respect to Garlic group.

Fig. 5. Mean values of one day expression of TNF-α by using RT-PCR assay in different treated groups.

Fig. 6. Mean values of seven days expression of TNF-α by using RT-PCR assay in different treated groups.
CAs assay after seven days of oral administration:

As indicated from table 1, oral administration of either garlic or olive oil alone to normal rats induced a non significant decrease in the mean values of all observed types of structural and numerical chromosomal aberrations when compared to that of normal control group. On the opposite side, the results of group 3 received CsA alone and group 7 received CsA plus garlic induced a significant increase (P<0.05) in the mean numbers of ring chromosomes, centromeric attenuation, total structural CAs, polyploidy, endomitosis and total numerical chromosomal aberrations as compared to normal control (group 1), vehicle control (olive oil) (group 2), and garlic alone (group 5).

Mitotic index (MI):

Table 2 represents the percentage of mitotic indices recorded after one and seven days of oral administration of different treatments alone or combined together. A non significant change in the percentage of mitotic indices in bone marrow cells was recorded after one and seven days oral administration of CsA alone, CsA plus garlic as compared with that of the normal control, vehicle control (olive oil), and garlic groups.

Table 2. Mitotic activity percentage recorded in rat bone marrow cells after one day and seven days of oral administration of different treatments alone or combined.

<table>
<thead>
<tr>
<th>No. of animals</th>
<th>One day</th>
<th>seven days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olive oil</td>
<td></td>
<td></td>
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<tr>
<td>Garlic</td>
<td></td>
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<tr>
<td>CsA</td>
<td></td>
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<tr>
<td>AZM</td>
<td></td>
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<tr>
<td>CsA + AZM</td>
<td></td>
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<tr>
<td>CsA + garlic</td>
<td></td>
<td></td>
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<tr>
<td>AZM + garlic</td>
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<td>CsA + AZM + garlic</td>
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</table>

Molecular results:

The expression levels of TNF-α (Figs 5&6) was highest in the group received garlic as compared with the values of the control group or olive oil only while group received CsA only showed great reduction in the expressed TNF-α in both one day and seven days of oral administration.

DISCUSSION:

In the present study, oral administration of 25 mg/kg of CsA alone for seven days showed genotoxic effects. That was determined by several cytogenetic parameters such as a statistically significant increase in the total chromosomal aberrations and in the number of abnormal metaphases.

These results are in line with the study reported by Palanduz et al. (1999) who showed that CsA has a genotoxic potential on human lymphocytes. Some previous studies reported that CsA did not induce genetic damage in a number of test systems (e.g., gene mutations in prokaryotes, gene mutations and chromosomal aberrations in cultured mammalian cells, chromosomal aberrations and micronuclei in rodent bone marrow cells (Zwanenburg and Cordier, 1994). Other studies reported that CsA causes sister-chromatid exchanges in human lymphocytes in vitro, unscheduled DNA synthesis and chromosomal aberrations in the peripheral blood lymphocytes of kidney transplant patients treated with CsA and prednisolone (IARC, 1990). The induction of genetic damage by CsA may be due to the oxidative stress caused by CsA that leads to the structural and functional damages in the tissues (Türk et al., 2007; Shakiba et al., 2009). It was suggested that CsA increases reactive oxygen species (ROS) that is hallmark of oxidative stress (Shakiba et al., 2009). The excess production of ROS by CsA may be explained by its ability to produce alterations in mitochondria by blocking the permeability transition pore (Nicolli et al., 1996), originating an increase in mitochondrial Ca$^{2+}$ concentration (Fournier et al., 1999), and alterations in mitochondrial electron transport chain. Nevertheless, the ROS generation may not be exclusive to the mitochondrial level, since CsA is metabolized by cytochrome P-450 3A that can also generate ROS (Serino et al., 1994). High ROS levels may thus induce mitochondrial DNA (mtDNA) damage and results in nuclear DNA fragmentation and increased apoptosis (Venkatesh et al., 2010; Kumar et al., 2012). By time, the presence of mitochondrial dysfunctions may exert cellular detrimental effects leading to imbalances in energy production, modulation of apoptosis, or redox maintenance (Wallace, 1994).
In the present study, oral administration of garlic alone for one and seven days had no significant increase in the numbers aberrant cells or decreased in the mitotic index in bone marrow cells of rats when compared to normal control group. On the other hand, oral administration of garlic combined with CsA and/or AZM after one and seven days did not give any significant reduction in the number of aberrant cells as compared to the normal control group. The obtained results agree with the studies which suggested that administration of garlic extract daily for at least 30 days was protective against the clastogenic effect (Das et al., 1995; Sengupta et al., 2002). Also, oral administration of olive oil alone did not change the mitotic index and did not induce chromosomal aberrations when was compared with the respective control group. These results agree with the study reported by (Evangelist et al., 2004). Moreover, the present study showed that oral administration of AZM alone and AZM plus garlic showed no significant changes in all types of structural and numerical chromosomal aberrations after one and seven days. Amacher et al. (1993) made an assessment in male and female mice with a single oral dose of 200 mg/kg of AZM followed by sacrifice after 24 or 48 h. They concluded that AZM did not cause gene mutation in microbial or mammalian cells, or chromosomal aberrations in cultured human lymphocytes or in mouse bone marrow in vivo. The present study agrees with this conclusion. Furthermore, our results revealed that the significant increase in the incidence of chromosomal aberration in bone marrow cells in combination group of CsA + AZM (for one and seven days), was due to the effect of CsA only because AZM was shown previously to have remarkable side effects and does not affect levels of CsA (Tokgöz et al., 2004). Here, a non significant change in the mitotic indices was detected of bone marrow cells in different groups after one and seven days of oral administration. This is in line with Tannuri et al. (2008), who observed that CsA was cytotoxic in growing animals, but did not change the mitotic index when compared with the control group.

The biochemical results revealed that oral administration of CsA caused increasing levels of AST, ALT, GGT, LDH, and ALP. These results were consistent with a study which suggested a reduction in the activity of one or more antioxidant systems due to direct toxic effect of CsA. CsA increased level of lipid peroxidation and oxidative stress and liver toxicity consequently (Türk et al., 2007). Lipid peroxidation is a chemical process initiated by free radicals (Ozaras et al., 2003) and an important mechanism in liver damage (Barón and Muriel, 1999).

Also oral administration of CsA+AZM showed significant increase in serum AST, ALT, GGT, LDH, and ALP. This is may be due to the damaging effect of CsA to hepatocyte membrane of CsA rather than the combination effect. On the other hand, oral administration of AZM alone showed significant increase in serum AST activities. Our results were similar to those obtained by Suriaiwnata and Min (2002), who observed that the AZM treatment led to a significant increase in the serum AST. Further, oral administration of AZM alone showed non significant changes in serum ALT, GGT, LDH, and ALP activities. This is similar to data discussed by Tokgöz et al. (2004) who noted that after AZM therapy, serum ALT, GGT, LDH, and ALP activities did not change significantly.

Oral administration of CsA alone showed non significant changes in serum total protein. The above results disagree with Rezzani et al. (2005), who observed that oral administration of CsA induce hepatotoxicity by inhibition of protein synthesis but with dose (7.5mg/kg) for 33 days that is different from our study. On the opposite side oral administration of CsA + garlic and CsA + AZM+ garlic showed significant increase in serum total protein. sharawary et al. (2009) noted that administration of garlic prevent liver damage of rat due to its ability to reduced free radical induced oxidative liver damage. Also results revealed that oral administration of CsA alone, CsA + AZM, CsA + garlic and CsA + AZM + garlic showed non significant changes in serum albumin after one and seven days. Jeon and Kim (2011) reported that oral administration of CsA (100 mg/kg/day) for 21 days causes marked decreases in serum albumin. On the other hand oral administration of CsA alone CsA + garlic showed significant increase in serum globulin. Our results agree with Rezzani et al. (2005), who showed that CsA-induced hepatotoxicity is characterized by increase in serum globulin, decline in GSH, glutathione peroxidase and catalase concentrations also oral administration of CsA + AZM and CsA + AZM + garlic showed significant increase in serum globulin. This might attributed to the direct hepatotoxic effect of CsA rather than combination effect.

Data presented that oral administration of CsA alone showed significant increase in
serum creatinine and BUN after seven days. These observations agree with other publications who demonstrated significant changes in renal function parameters in both patient and experimental animals following by administration of CsA (Amudha et al., 2007; Ishikawa and Homma, 2012). Alterations in renal haemodynamic, glomerular and/or tubular structures, including inflammation have all been reported to play an important role in CsA induced renal dysfunction (Wongmekiat et al., 2008). The damage to the glomeruli and tubules in CsA mediated toxicity was facilitated through the expression of c-myc. This expression of c-myc in turn reflects the increased apoptotic death of the cells (Chakravarthi et al., 2010). On the other hand, oral administration of AZM alone showed non significant changes in serum creatinine and BUN. Our results agree with that by (Tokgöz et al., 2004), who demonstrated that after AZM therapy; serum creatinin and BUN did not change significantly. It may be used safely since it does not have remarkable side effect and does not affect on the level of creatinine (Wirnsberger et al., 1998; Tokgöz et al., 2004). Also oral administration of CsA + AZM showed significant increase in serum creatinine due to the reduction of renal perfusion induced by CsA than effect of combination.

Oral administration of CsA alone showed significant increase in serum glucose after seven days. Our results were agreed with (Böhmer et al., 2010), who observed that CsA is involved in glucose homeostasis, and reinforcing reports that long-term CsA treatment affects glucose homeostasis, by decreasing serum insulin levels, increasing peripheral insulin resistance and serum glucose levels (Hjelmesaeth et al., 2005; Penfornis and Kury-Paulin, 2006). The effect on insulin levels may result from compromised insulin production either via β-cell toxicity or via inhibition of DNA synthesis (Penfornis and Kury-Paulin, 2006). On the other hand, oral administration of CsA + AZM and CsA + AZM + garlic showed significant increase in serum glucose after seven days due to the reduction of renal perfusion induced by CsA than effect of combination, while oral administration of AZM alone showed a non significant change in serum glucose. From all biochemical parameters, the clear drug-drug interaction between CsA and AZM were little to be nearly absent this may be due to the difference between them in the metabolic pathway. There were no available publication studied the interaction between them at the level of biochemical parameters. In humans the immunosuppressive drug CsA has been used successfully in organ transplantation and in the treatment of autoimmune disorders. The drug, however, causes side effects that occur mainly in the kidney but also in the liver. Although, the mechanisms leading to the hepatic side effects are not fully understood, several reports have strongly suggested that reactive oxygen production is a common mechanism of drug toxicity (Wolf et al., 1997) reported that CsA in primary rat hepatocyte cultures caused a concentration-dependent increase of free reactive oxygen species. CsA mediated reactive oxygen species formation. Therefore, garlic may have a protective effect on the deteriorated hepatic function resulting from oxygen free radicals in the CsA-induced hepatotoxicity. There were significant increases in ALT, AST, GGT levels in group, suggesting a significant hepatotoxicity due to oxygen free radicals. Garlic treatment significantly protected some parameters in hepatic function such as (ALT, GGT, LDH and globulin), kidney function such as (creatinine) and free radical- mediated injury in the liver and kidney against CsA-induced changes. The results in this experiment suggest that garlic may be effective in preventing the CsA-induced hepatotoxicity and nephrotoxicity without changing plasma CsA levels in a rat model.

Regarding to figures 5 & 6, the results of RT-PCR assay revealed that the group received CsA alone for one and seven days has lowest group in TNF-α gene expression. The present results agree with Ciesielski et al. (1997) who mentioned that in rats treated with CsA, TNF-α levels were lower than in rats receiving no preventative treatment linking CsA with the prevention of cell death in addition to inhibition of T cell proliferation. CsA act by forming a complex with immunophilin, which inhibits the Ca2+/calmodulin-dependent serin-threonine phosphatase calcineurin. Inactive calcineurin is unable to activate the nuclear factor of activated T cells (NFAT) (Eckstein et al., 2005; Leitner et al., 2011). TNF-α gene expression was lower in the group received AZM alone when compared with normal control group. This result is in line with Hall et al. (2002) and Tong et al. (2011), who observed that AZM administrated at lower doses than the minimum inhibitory concentration, reduced the serum levels of TNF-α, IL-6 and IL-8 and inhibited epithelial cell-mediated neutrophil survival by release of growth factor (GM-CSF). Inhibitory actions of AZM may be related to effects on the transcription factor, NF-KB, which is activated by a wide variety of inflammatory stimuli and mediates the expression of genes for many inflammatory mediators (Barnes and Karin 1997). According to the results of RT-PCR assay, the group that received garlic alone for one and seven days was the highest in TNF-α gene expression. The present results agree with Sumiyoshi (1997) who showed that treatment with garlic extracts improved the activation of natural killer cells, the function of T- lymphocytes and the level of IL-2. Also in
vitro and in vivo studies showed that aged garlic extracts stimulate immune functions (Chetty et al., 2004).

From the present study we conclude that CsA was genotoxic on chromosomes and TNF-α gene, administration of CsA should be with great medical care for different organs.

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دراسة وراثية خلوية وجنينية لتفاعل السيكلوسييردين والأيزوبريميسين مع اختبار حماية الجين

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قسم علم الحيوان، كلية العلوم، جامعة القاهرة

كلية الطب البشري، جامعة القاهرة

* يهدف هذا البحث إلى دراسة تأثير كل من السيكلوسييردين (A) والأيزوبريميسين وكلا التفاعلات بينهما على درجة التناسق المورفي لجين إنزيم تروكسين (T) في الحيوان. التأثير على المسؤوليات الجينية والكيميائية لجهاز الدماغ. التأثير على سلسلة AT8 في الخلايا الجودية. التأثير على سلسلة AT8 في الخلايا الجودية. التأثير على سلسلة AT8 في الخلايا الجودية.

** عادةً ما يكون بالإفراط في ذلك وعند الخضرة الأول والثاني، في الفسيولوجيا المعرضة ومتغيرة.