OPEN ACCESS
Advances in Animal and Veterinary Sciences

Research Article

Effect of Alcoholic Extract of *Salvia officinalis* Leaves on some Physiological Parameters Aspects in Acrylamide-Treated Rats

Khalisa Khadim Khudiar*, Ghasag Jawad Hussein

Department of Physiology and Pharmacology, College of Veterinary Medicine, University of Baghdad, Iraq.

Abstract | This study was carried out to explore the effects of alcoholic extract of *Salvia officinalis* (SO) leaves on some physiological parameter including: protein profile, antioxidant status,some immunological and proinflammatory biomarkers in acrylamide (ACR) comparing to cyclosporine (Cys) treated rats. Thirty adult male rats were selected randomly and equally allocated into six gropes and treated daily for 45 days with oral manner as follow: Group G1: (control group) received tap water), G2: rats in this group were received (150 mg/kg /B.W) of alcoholic extract of SO leaves,G3: rats of this group were received (1 mg/kg /B.W) of acryl amide in drinking water, G4: rats in this group were received (1mg/kg /B.W) of cyclosporine, G5: rats in this group were received (150 mg/kg /B.W) of *Salvia officinalis* leaves extract and acryl amide(1 mg/kg /B.W), G6: rats in this group were received the same mentioned dose of SO and cyclosporine as in G2 and G4 groups. At the end of experiment, animals were sacrificed and blood was drawn by cardiac puncture technique for measuring the following parameters: serum reduced glutathione (GSH), peroxynitrite radical, total protein, albumin, globulin concentrations as well as phagocyte index (%) and mitotic index (%). Serum immunoglobulin G (IgG), interleukin-6 (IL-6) and C – reactive protein (CRP) concentrations were also recorded. The results of the current study revealed the beneficial effect of alcoholic extract of *Salvia officinalis* against deleterious effect of ACR and cyclosporine illustrated by its antioxidant, immunostimulatory and anti-inflammatory effect. Significant increase in serum TSP, albumin and globulin concentration, as well elevation in serum GSH and depression in peroxynitrite radical concentration was observed after oral intubation of SO alone or in combination with ACR or Cys comparing to the ACR or cyclosporine treated rats which showed controversial result. Concerning immune-stimulatory and anti-inflammatory effect of *Salvia officinalis*, significant elevation in phagocytic index % (PI), mitotic index % (MI) and in serum (IgG), as well as significant depression in serum IL-6 and CRP concentrations was observed following extract intubation comparing to the immune-supperion and pro inflammatory effect of ACR and cyclosporine. On conclusion, alcoholic extract of *Salvia officinalis* (SO) leaves alleviate the detrimental effect of ACR and cyclosporine correlated with their pro oxidative, immune suppressive and pro-inflammatory effect. Non-significant differences between ACR and Cys were observed in all measure issue.

Keywords | *Salvia officinalis,* Cyclosporine, Acrylamide, Phagocytic index, Mitotic index, IgG

Editor | Kuldeep Dhama, Indian Veterinary Research Institute, Uttar Pradesh, India.
Received | November 21, 2016; **Accepted** | January 20, 2017; **Published** | January 24, 2017
***Correspondence** | Khalisa Khadim Khudiar, Department of Physiology and Pharmacology, College of Veterinary Medicine, University of Baghdad, Iraq; **Email:** khaliaskhadim@gmail.com
Citation | Khudiar KK, Hussein GJ (2017). Effect of alcoholic extract of *Salvia officinalis* leaves on some physiological parameters aspects in acrylamide-treated rats. Adv. Anim. Vet. Sci. 5(1): 47-55.
DOI | http://dx.doi.org/10.14737/journal.aavs/2017/5.1.47.55
ISSN (Online) | 2307-8316; **ISSN (Print)** | 2309-3331

INTRODUCTION

Salvia officinalis (garden sage, common sage) or Dalmation sage enjoys the reputation of being a panacea because of its wide range of medicinal effects. The genus *Salvia* is one of the most important genera in the Labiatae family and includes over 900 species all over the world. Salvia species are aromatic plants, rich in essential oils which have been used in food, cosmetics, perfumes and pharmaceutical products (Pop et al., 2014). The plant antioxidant (Anamaria et al., 2013), antinociceptive and anti-inflammatory (Arraiza et al., 2012; Rodrigues et al.,

2012) and diuretic (Bhadoriya et al., 2011) activities are recorded. In addition, to its anticancer (Russo et al., 2013) and antidiabetic effects (Hajzadeh et al., 2011).

Acrylamide (ACR) is a reactive, small organic molecule with very high water solubility. These properties facilitate its rapid absorption and distribution through the body (Manna et al., 2006). ACR has become one of the major public health concerns since it was detected in widely consumed food items for example, fried bread (breakfast cereals), potato chips, and any carbohydrate-rich food items cooked at high temperatures (higher than 200°C) (Devi et al., 2014). The harmful effects of acrylamide have been proposed to be caused by its neurotoxicity (Zhang et al., 2011), mutagencity and carcinogenicity (de Woskin et al., 2013) as well as oxidative stress (Venkataswamy et al., 2015). Researches also reported toxic effect of ACR on reproductive (Nixon et al., 2014), and skeletal muscle (Al-Serwi and Ghoneim, 2015). Beside, acrylamide-induced locomotors defects and neurotoxicity are associated with Parkinson's disease (Li et al., 2016).

Cyclosporine A (Cys) is a fungal metabolite with potent immunosuppressive properties. It down-regulates the production of interleukin-2 by T lymphocytes (Bleyzac et al., 2014) affecting both T helper and T effector cell functions (Wu et al., 2013). Because of this action, Cys has been extensively used for the prevention of organ rejection in transplant patients as well as for the treatment of autoimmune diseases (Rezzani, 2004). Cyclosporine A inhibits the proliferation of human gastric cancer cells and can induce their apoptosis (Xing et al., 2016). Beside increased production of ROS, lipid hydroperoxides and a significant decrease in total antioxidants with Cys treatment confirms the role of oxidative stress in Cys induced organ toxicity (Ezejiofor et al., 2016).

Depending on the available information reveled that antioxidant supplementation protected the body against oxidative stress induced by different case including pollution, exposure to different oxidant and causing several diseased condition, inflammation and immunosuppression, the present study was designed to investigate the effect of alcoholic extract of *Salvia officinalis* against different aspects related to oxidative stress damage induced by ACR comparing to cyclosporine.

MATERIALS AND METHODS

Preparation of Ethanolic Extract of *S. officialis*

Twenty g. of *Salvia officialis* powdered leaves were taken and extracted with soxhlet apparatus ethanol 70%. The solvent was removed under reduced pressure in a rotary evaporator until they become completely dry. The residue was stored at 4°C for further use (Harborne, 1984).

Animals and Experimental Design

Thirty mature male Wistar rats (aged 90 days and weighted 190±10 g), were allowed to acclimatize to the animal house environment before beginning of the experiment. Animals were housed in polypropylene cages inside a well-ventilated room. Male rats were fed on the standard chow and drinking water *ad libitum* throughout the experiment. Room temperature was maintained at 23±2°C, the light-dark cycle was on a 12 hr. light/dark cycle with light on at 06:00 p.m. and off at 06:00 a.m. during the experimental periods. Rats were randomly selected and equally divided in to six groups as follows G1, G2, G3, G4, G5 and G6. They were treated orally (daily) for 45 days as follows G1: control group, were given distilled water G2: rats of this groups were given *Salvia officinalis* (150 mg/Kg B.W.) G3, rats of this groups were received acrylamide (1 mg/kg B.W.), G4, rats of this groups were given cyclosporine (1mg/Kg B.W.) for 45 days, G5, rats of this groups were given orally *Salvia officinalis* and acrylamide (1 mg/kg B.W. +150 mg/kg B.W.) daily for 45 days, G6, rats of this groups were given orally *Salvia officinalis* and cyclosporine (1 mg/kg B.W. +150 mg/kg B.W.) daily for 45 days.

Blood samples were collected at end of experiment, blood was drawn by cardiac puncture technique from anesthetized rats. Then serum samples were separated and frozen at -20°C until analysis of the following parameters: Serum total protein and albumin concentrations was measured using total protein and albumin kits (Biomaghreb- Germany) immunoglobulin G (IgG) concentration was measured using IgG kit ELISA (Hcusabio- China) serum peroxynitrite radical concentration was determined according to (Vanuffelen et al., 1998) reduced glutathione (GSH) concentration was measured according to (Burtis and Ashwood, 1999). Furthermore, determination of bone marrow cellularity (Mitotic index %) has been determined as described by Savage (1975) and determination of Phagocytic Index % according to Weber and Osborn (1982). Serum Interluekin-6 (IL6) concentration was measured using ELISA Interluekin-6 kit (RayBio-USA), also C-Reactive protein (CRP) concentration was estimated by using CRP kit (Spectrum-UK). Statistical analysis of data was performed according for One-Way analysis of variance (ANOVA) utilizing a significant level of ($P<0.05$) specific groups differences were identified utilizing least significant differences (LSD) as described by Snedecor and Cochran (1973).

RESULTS

The results in Table 1 showed that oral intubation of *Salvia officinalis* alone (G2 group), or concurrently with acryl amide in drinking water (group G5) or cyclosporine (group G6) caused significant elevation ($P> 0.05$) in serum GSH and significant decrease ($P<0.05$) in serum peroxyni-

trite concentration comparing to the value in Acryl amide (group G3) or cyclosporine (G4) treated groups. A statistical analysis indicated that the mean values of TSP and albumin concentration is significantly decreased (P<0.05) after Acryl amide exposure or cyclosporine treatment for 45 days comparing to the value in other treated groups. on the other hand serum TSP and albumin concentration significantly increased (P<0.05) after oral intubation of *Salvia officinalis* to normal, acrylamide or Cys treated groups comparing to the value in G3 and G4 treated groups (Table 1). Significant increase (P>0.05) in serum globulin concentration was observed after oral intubation of *Salvia officinalis* concurrently with acrylamide or cyclosporine comparing to the value in G2,G3 and G4. The value in group G5 and G6 tend to normalize that of the control at the end of the experiment (Table 1).

The results in Table 2 showed a significant increase (P<0.05) in phagocytic index % and MI% index after exposure to acrylamide (G5) and oral intubation of cyclosporine (G6) concurrently with *Salvia officinalis* comparing to the value in G3 and G4 groups which received acrylamide or cyclosporine alone which showed significant (P<0.05) depression in these parameters. Oral intubation of *Salvia officinalis* to normal (G2), or concurrently with acrylamide (G5) or cyclosporine (G6) treated groups showed significant (P<0.05) increase in serum IgG concentration as compared to G3 and G4 groups (Table 2). The results also showed that oral intubation of *Salvia officinalis* to normal (G1), G2, SO+ACR(G5) and SO+ Cys (G6) treated groups caused significant increase (P<0.05) in IL-6 and CRP concentration comparing to the value in ACR (G3) and Cys (G4) groups (Table 2).

DISCUSSION

Effect of *S. Officinalis* on Total Serum Protein Concentration in Acrylamide or Cyclosporine Treated Rat

Here in study indicated that treatment with alcoholic extract of SO concurrently with ACR or Cys caused significant increase in TSP, albumin and globulin concentration comparing to Cys and ACR treated rats. Such result demonstrated the hepatoprotective activity of *Salvia officinalis* and thus supports the usage of this plant for treatment of liver disorders (Parsai et al., 2014). Sage constituents with their antioxidant properties overcame the lower in the total protein content perhaps by preventing oxidative stress and protein fragmentation and enhancing protein synthesis (Durling and Catchpole, 2007). Depression in protein carbonyl content (an indicator for cellular protein oxidation) after SO supplementation (Osman and El–Azime, 2013) could be a mechanism for elevation serum protein.

Table 1: Effect of ethanolic extract of *Salvia officinalis* on serum GSH, peroxynitrite, total albumin, globulin and albumin concentration in normal, acrylamide and cyclosporine treated rats

Group	G	G2	G3	G4	G5	G6
Parameter						
Reduce GSH	55.58±0.4 B	58.208±0.7 A	42.786±0.7 D	44.994±1.2 D	50.228±0.8 C	51.05±0.5 C
Peroxynitrite radical	31.63±0.6 D	28.89±0.7 E	40.896±0.5 A	40.474±0.8 A	33.39±0.6 C	34.76±0.6 B
Total protein	6.608±0.2 A	7.577±0.6 A	5.616±0.7 B	5.531±0.8 B	6.264±0.7 A	6.27±0.6 A
Albumin	2.41±0.03 B	3.122±0.1 A	1.81±0.1 D	1.85±0.02 D	2.19±0.02 C	2.16±0.02 C
Globulin	4.198±0.1 A	3.935±0.1 B	3.806±0.1 B	3.681±0.02 C	4.074±0.02 A	4.11±0.02 A

Values expressed as mean ± SE; **n:** 5; Different capital letter represent a significant difference between groups (p <0.05) *vs.* Control; **G1:** Control; **G2:** *Salvia officinalis* (150mg/kg B.W); **G3:** Acryl amide (1mg/kg B.W); **G4:** Cyclosporine (1mg/kg B.W); **G5:** *Salvia officinalis* (150mg/kg B.W) + Acryl amide (1mg/kg B.W); **G6:** *Salvia officinalis* (150mg/kg B.W) +A cyclosporine (1mg/kg B.W)

Table 2: Effect of ethanolic extract of *Salvia officinalis* on phagocytic index (%), mitotic index (%) and serum immunoglobulin G (IgG), interlukin-6 (IL-6) (pg /ml) and C-reactive protein (CRP) concentrations in normal, acrylamide and cyclosporine treated rats

Group	G	G2	G3	G4	G5	G6
Parameter						
Phagocytic index	22.4±0.3 B	26.68±0.7 A	16.62±0.3 C	15.52±0.2 D	21.42±0.4 B	21.32±0.2 B
Mitotic index	23.726±0.7 B	28.008±0.5 A	16.71±0.3 D	15.42±0.3 E	22.022±0.3 C	22.654±0.7 C
IgG	4.38±0.09 B	4.75±0.2 A	3.21±0.07 B	3.23±0.05 B	4.77±0.07 A	4.90±0.1 A
IL-6	22.64±0.2 B	24.45±0.4 A	28.99±0.4 D	29.42±0.3 D	21.63±0.2 C	21.59±0.2 C
CRP	6.94±0.3 C	7.97±0.3 A	10.98±0.05 D	10.91±0.1 D	7.52±0.1 B	7.40±0.2 B

Note: For details see Table 1

Significant decreases of the total protein, albumin, and globulin levels reported in the current study after exposure to ACR are going in line with study by Hammad et al. (2013) and Mahmood et al. (2015). A steady decrease in hepatic protein levels with higher doses of ACR could be attributed to retarded protein synthesis, change in protein metabolism, or to the leakage of protein reserves from hepatocytes (Asha et al., 2008). Significant decrease of serum albumin and TSP were noticed after 2 weeks of treatment with Cys (Elsayed et al., 2016) that indicated hepatotoxicity (Kienhuis et al., 2013). Based on *in vitro*, cyclosporine could inhibits hepatic protein synthesis and then depression in protein, probably at the translation level (Jeon and Kim, 2011). Besides, over production of ROS after Cys exposure (Mostafavi-Pour et al., 2013) may accompanied decrease in liver protein level (Gala´n et al., 1999) and then depression in serum.

Effect of Acrylamide on Serum Antioxidant Status (Glutathione and Peroxynitrite Radical Concentration) in Normal, Acrylamide or Cyclosporine Treated Rats

Significant elevation in serum GSH and depression in peroxynitrite radical concentration after oral intubation of *Salvia officinalis* indicated its antioxidant capacity. Antioxidant and free radical scavenging activity of alcoholic and water extract of SO were studied *in vivo* (Oboh and Henle, 2009) and *in vitro* (Wielgus et al., 2011; Petrova et al., 2015) study as well as in SO nanoparticles (Wagdy and Faiza, 2013), Carnosic acid, carvacrol, thymol (Tenor et al., 2011) α-thujone and camphor (Pop et al., 2014) as well as rosmarinic acid and its dimer (salvianolic acid), showed a high antioxidant activity and is a very significant scavenger of free radicals (Hamidpour et al., 2014). The ability of sage to increase basal GSH levels and depressed peroxynitrite concentration could be probably due to induction of glutathione synthesis (Horthov et al., 2015) and scavenging the nitrogen oxide or their radical derivatives with depression in peroxynitrite level (Alkan et al., 2012).

The current study showed significant decrease in serum GSH concentration and elevation in peroxynitrite radical concentration after ACR treatment indicating a case of oxidative stress, which is in line with recent study reported by Abd El-Ghaffar et al. (2015), Al-Agele and Khudiar (2016) and Sabeeh (2016) in rats. Acrylamide is well known to generate free radicals, induce lipid per oxidation disturbing the antioxidant status and ultimately leading to oxidative stress (Zhang et al., 2013; Abdel-Daim et al., 2015). Accumulation of free radicals such as superoxide, NO after ACR exposure can react together to produce peroxynitrite, the highly reactive oxidizing agents have the ability to attack and damage cell membranes and biomolecules (Song et al., 2013).

It has been shown that Cys toxicity in kidney, liver and nervous system is accompanied by increased both H_2O_2 production and lipid peroxidation, and concominantly decreased cellular level of reduced glutathione (Uz et al., 2012). Reduction in the content of protein sulfhydryl groups and formation of protein thiol oxidation by Cys (Wolf et al., 1997), leading to GSH depletion (Tirkey et al., 2005), could be another possible mechanism. It has been demonstrated that Cys-induced local production of hydroxyl radical, a highly active and detrimental radical, with elevation in superoxide radical (De Lema et al., 1997) could be attributed to production of peroxynitrite radical.

Effect of *S. officinalis* on Phagocytic Index (%) in Acrylamide or Cyclosporine Treated Rat

The present study demonstrated significant increase in phagocytic index after oral intubation of SO concurrently with ACR or Cys treated rats which showed significant decrease indicating immune stimulatory effect of SO. Active component of SO (essential oil) caused an elevation in blood phagocytic activity in rabbits (Szabóová et al., 2008), and in broiler chickens (Ryzner et al., 2013). Water soluble polysaccharide are active SO compound are claimed to possess immune modulatory activity (LoPachin et al., 2003), including anti-inflammatory, macrophage phagocytic stimulation and induction of cytokine as well as mitogenic activity (Abou Donia et al., 1993). While numerous studies revealed that macrophage functions, e.g. phagocytic activity, chemotactic migration, superoxide and peroxide production and protein secretion, to be reduced in the presence of Cys (Svensson et al., 1995).

Effect of *S. officinalis* on IgG Concentration in Acrylamide or Cyclosporine Treated Rats

Elevation in serum IgG concentration after SO supplementation improved immunostatus of the body and reflected its boosting the humeral immune response.

Many protective function of immune cells depend upon the fluidity of cell membrane, depression in fluidity of membrane by LPO -induced by many toxicant (including ACR) lead to marked atrophy of thymus and B cell dysfunction (Bendich, 1990). So intake of dietary antioxidant enhance body immunity and protect it from harmful effect of FRs and oxidative stress (Sadek, 2012) that could be induced by ACR. Active compounds of sage extract act on augmentation of humeral and cellular immune response. Through its effect on neutrophil, macrophage, B and T lymphocyte. These active compounds act synergistically or separately in enhancing responsiveness of these cells directly or indirectly (Mukul Das and Prahlad, 1982). Significant decrease in serum IgG concentration after ACR exposure indicating toxic effect of ACR on humeral immune function (Jin et al., 2014). A lot of information pointed to the role of FRS

that could be produced after ACR exposure in affecting immune-defence mechanism and weakening of immunity (Ivanov, 2008). Immune suppression effect of cyclosporine is depicted in some situation (Rezzani, 2004; Wu et al., 2013).Cyclosporine treatment completely or partially abrogated IgG production in rat model (Jones et al., 1988) and human (Weber et al., 1991). Treatment of hamster with Cys and prednisolone lowered levels of circulating IgG against worm crude antigen (Costa Dias et al., 2013).

Effect of *S. officinalis* on Mitotic Index % in Acrylamide and Cyclosporine Treated Rat

Significant increase in percentage of mitotic activity after treatment with Salvia water extract in low concentrations was recorded by Gateva et al. (2015) indicating its anti-mutagenic effect (Bouaziz et al., 2015). Sage extract caused significant increase in bone marrow mitotic index in mice comparing to cystosor (Al-Ezzy et al., 2010). On the contrary, different result were observed by others, where prolong use of high concentration of plant may increase its mutagenic toxic material (Al-Joubori et al., 2014), delay cell division (Burim et al., 1999) leading to decrease in MI%. Polysaccharides (mutagenic agent) and other active component of SO have been found to stimulate the immune function of bone marrow cells by inducing cell division (Capek and Hribalova, 2004) presence of mutagenic compound in the extract might be related to its action on spindle assembly or cell cycle regulator (Al-Moaruf et al., 2004). Besides, Cytogenetic effect of plant may be due to its ability to act as FR scavenger so it can captures ROS release from toxic substance like ACR (Liping et al., 2007).

ACR cytotoxicity indicated by decrease in MI % and genotoxicity could be occur due to decreasing in oxidative defense system (Zamorano-Ponce et al., 2006), as well as elevation in ROS production and its known to be clastogenic and mutagenic *in vivo* and *in vitro* (da Costa et al., 2003). Reduction in MI after ACR could be due to DNA damage and inhibition of DNA synthesis (Nixon et al., 2012), and blocking of cell from entering mitosis (Tülay and Ozlem, 2010). General speaking MI could be disrupted either by inhibitory process of cell division, disturbing normal function of mitotic spindle and producing chromosomal aberration lead to reduction in mitosis (Haroun and Al-Shehin, 2001). Beside increase in number of interphase or dead cells leading to its accumulation, induced DNA damage (Zhang et al., 2009) by ACR could be claimed.

Significant decrease in MI activity after Cys treated indicated its mutagenic activity. cyclophosphatimide treatment has been shown to cause an elevation of micronuclei function in bone marrow of mice and significant decrease in interphase index (MI) (Al-Naimy et al., 2010). This may be due deleterious effect of Cys on bone marrow cell due its free radical producing activity, or it may be due to defect in mitotic spindle composition during cell division (Srivastava et al., 1983) and consequently causing mitosis deficiency (Catalgol et al., 2009). Cyclosporine is thought be decrease breakage of Anaphase Bridge during cell division and DNA damage (Indran et al., 2008). Furthermore, Cyclosporine may cause abnormalities in lymphocyte receptor involved in mitagenic recognition, resulting in inhibition of blastogenic and mitotic index (Oduola et al., 2007).

Effect of *S. officinalis* on IL-6 and CRP Concentration in Acrylamide or Cyclosporine Treated Rat

Reduction in serum IL-6 and CRP concentration after SO supplementation indicating the anti-inflammatory effect of the sage (Tabl et al., 2014; de Melo et al., 2012). Supplementation of *Salvia officinalis* cause significant decrease in CRP concentration in healthy comparing to obese patient (Hernandez-Saavedra et al., 2015). Increased circulating lipids due to obesity lead to an increased inflammatory state, through an augmented production of cytokines (Mathieu et al., 2010) like IL-6 as well as CRP (Devaraj et al., 2009), accordingly, hypolipidemic and the anti-inflammatory effect of SO could reduce CRP and IL-6 level. The impact of elevation in serum IL-6 concentration after exposure to ACR in the current study are in line with those of (Zhang et al., 2013; Abdel-Diam et al., 2015). IL-6 is labeled as anti-inflammatory as well as pro-inflammatory mediator (Scheller et al., 2011) and can modulate immunosuppressive functions (Hegde et al., 2004). Oxidative stress induced after ACR exposure drives proinflammatory cytokine expression (Szalowska et al., 2013) like IL-6 may be attributed to its elevation. Different doses of ACR (15-50 mg /kg B.W) caused significant increase in CRP concentration in rats exposed to low fat diet comparing to those kept on high fat diet and control (Jin et al., 2016). This could be related to the lowering of the reserves of an important cellular antioxidant, GSH, by acrylamide (Naruszewicz et al., 2009). An elevation in CRP and IL-6 serum levels regarded as propensities value in assessing progression of some chronic disease like coronary heart disease (CHD) (Lopez et al., 2006), which are expected to occur following exposure to ACR (Totani et al., 2007). Besides, their elevation is an indicator of infection in immune suppressed subject (Pepys and Hirschfield, 2003; Guillermo and Doscoteaux, 2014). The result of the current study showed significant increase in serum IL-6 and CRP concentration after cyclosporine treatment comparing to SO. Patients with immune suppression therapy have been shown to have elevated level in the serum IL-6 (Tilg et al., 1992). The pro-inflammatory effect of Cys (Waters et al., 2005) and its effect on expression of IL-2 drives IL-6 secretion (Musso et al., 1992) was documented. In contrast to the current result long term treatment (more than one

year) with cyclosporine caused significant decrease in serum IL-6 (Hanudle et al., 2016) and CRP (Madhok et al., 1991). The discrepancy in the result may be reflected that toxic compounds response is under the influence of several mediation, in addition to the role of duration of exposure in philosophy of result discussion.

ACKNOWLEDGMENTS

Authors of this study would like to thank College of Veterinary Medicine, University of Baghdad, Iraq for their support.

CONFLICT OF INTEREST

There do not exist any conflict of interest.

AUTHORS' CONTRIBUTION

Khalisa Khadim Khudair designed the experiment . Ghasag Jawad Hussein analyzed and interpreted the data and performed the experiment. Khalisa Khadim Khudair gave technical support , wrote the paper and conceptual advice.

REFERENCES

- Abdel-Daim MM, Abd Eldaim MA, Hassan Abeerm GA (2015). *Trigonella foenum-graecum* ameliorates acrylamide-induced toxicity in rats: Roles of oxidative stress, proinflammatory cytokines, and DNA damage. Biochem. Cell. Biol., 93: 192-198. https://doi.org/10.1139/bcb-2014-0122
- Abd El-Ghaffar SK, Fiedan I, Ahmed E, Omar HED (2015). Acrylamide induced testicular toxicity in rats: Protective effect of garlic oil. Biomarkers .,1(10): 1-8. https://doi: 10.21767/2472-1646.100005
- Abou Donia, Ibrahim M, Corcoran J, Lack L, Friedman A, Lapadula M (1993). Neurotoxicity of glycidamide and acrylamide metabolite following intraperitoneal injection in rats. J. Toxicol. Environ. Health. 39: 447-464. https://doi.org/10.1080/15287399309531764
- Al-Agele FAL, Khudiar KK (2016). Effect of acryl amide and fructose on some parameters related to metabolic system in adult male rats. J. Pharma. Med. Biol. Sci. 4(1): 1-10.
- Al-Ezzy RM, Al-Samarrae K, Ad'haih AH (2010). Effect of sage (*Salvia officinalis*) aqueous extract on mitotic index in albino male mice. J. Biotechnol. Res. Center. 4(1): 36-42.
- Al-Joubori MA, Zaidan HK, Al-Saadi AH (2014). Evaluation of Chromosome Aberrations and mitotic index in alloxan-induced diabetic male diabetic male rats treated with the mixture of plants extracts mixture. J. Babylon Univ.: Pure Appl. Sci. 5 (22): 1545-1555.
- Alkan FU, Gürsel FE, Ateş A, Özyürek M, Güçlü K, Alyun M (2012). Protective effects of *Salvia officinalis* extract against cyclophosphamide-induced genotoxicity and oxidative stress in rats. Turk. J. Vet. Anim. Sci. 36(6): 646-654.
- Al-Moaruf OA, Muibat OB, Asiata OI, Isiaka AO, Nureni O (2004). Heavy trace metals and macronutrients status in herbal plants of Nigeria. Food Chem. 85: 67-71. https://doi.org/10.1016/j.foodchem.2003.06.004
- Al-Naimy EH, Al-Amery MM, Al-Azy RM (2010). Antibacterial and cytogeneic effect of *Cassia italica* leaf extract on albino male mice. J Al-Nahrain Univ. 13 (4): 132-139.
- Al-Serwi RH, Ghoneim FM (2015). The impact of vitamin E against acrylamide induced toxicity on skeletal muscles of adult male albino rat tongue: Light and electron microscopic study. J. Microsc. Ultrastruct. 3: 137–147. https://doi.org/10.1016/j.jmau.2015.09.001
- Anamaria P, Muste S, Mureşan C, Pop C, Salanţă L (2013). Comparative study regarding the importance of sage (*Salvia officinalis* L.) in terms of antioxidant capacity and antimicrobial activities. Hop Med. Plants. 1(2): 41-42.
- Asha S, Renu S, Jyotsna J (2008). Biochemical changes in the liver of Swiss albino mice orally exposed to acrylamide. Int. J. Sci. Tech. 2(3): 542-550.
- Arraiza M, Arrabal C, López JV (2012). Seasonal variation of essential oil yield and composition of sage (*Salvia officinalis* L.) grown in Castilla - La Mancha (Central Spain). Not. Bot. Horti. Agrobo. 40(2), 106-108.
- Bendich A (1990). Antioxidant vitamins and their functions in immune responses. In: Antioxidant nutrients and immune functions (eds. A. Bendich, M. Phillips, RP. Tengerdy). Plenum Press, New York. Pp. 33. https://doi.org/10.1007/978-1-4613-0553-8
- Bhadoriya U, Tiwari S, Sharma P, Bankey S, Mourya M (2011). Diuretic activity of extract of *Salvia officinalis*. Asian J. Pharm. Life Sci. 1 (1): 24-28.
- Bleyzac N, Philippe M, Bertrand A, Bertrand Y, (2014). Confounding effect of cyclosporine dosing when comparing horse and rabbit antithymocyte globulin in patients with severe aplastic anemia. Haematologica. 100: e211. https://doi.org/10.3324/haematol.2014.122275
- Bouaziz M, Yangui T, Sayadi S, Dhouib A, (2009). Disinfectant properties of essential oils from *Salvia officinalis* L. cultivated in Tunisia. Food Chem. Toxicol. 47: 2755–2760. https://doi.org/10.1016/j.fct.2009.08.005
- Burim RV, Candle R, Lopes JLS, Takahashi CS (1999). Genotoxic action of the sesquiterpene lactone glaucolide B on mammalian cells *in vitro* and *in vivo*. Genet. Mol. Biol. 22: 401-406. https://doi.org/10.1590/S1415-47571999000300020
- Burtis C, Ashwood E (1999). Textbook of clinical chemistry, 3rd Ed. London. Pp. 941. https://doi.org/10.1038/43589
- Capek P, Hribalova V (2004). Water-Soluble polysaccharides from *Salvia officinalis* L. possessing immunomodulatory activity. Phytochem. 65: 1983-1992. https://doi.org/10.1016/j.phytochem.2004.05.020
- Catalgol B, Ozhan G, Alpertunga B (2009). Acrylamide-induced oxidative stress in human erythrocytes. Hum. Exp. Toxicol. 10: 611-617. https://doi.org/10.1177/0960327109350664
- Costa Dias SR, Da Costa AFDV, Gazzinelli-Guimarães PH, Roatt BM, Fonseca KD, De Paiva NCN, Giunchetti RC, Carneiro CM, Fujiwara RT, Rabelom ÉML (2013). Prednisolone and cyclosporine A: Effects on an experimental model of ancylostomiasis. Exp. Parasitol. 133: 80–88. https://doi.org/10.1016/j.exppara.2012.10.008
- Da Costa GG, Churchwell MI, Hamilton LP, Von Tungeln LS, Beland FA, Marques MM, Doerge DR (2003). DNA adduct formation from acrylamide via conversion to glycidamide in

adult and neonatal mice. Chem. Res. Toxicol. 16: 1328–1337. https://doi.org/10.1021/tx034108e
•De Lema GP, Arribas-Gomez I, Ruiz-Gines JA, de Arriba G, Prieto A, Rodriguez-Puyol D, Rodriguez-Puyol M (1997). Reactive oxygen species mediate the effects of cyclosporine A on human cultured mesangial cells. Transplant Proc. 29(1-2): 1241-1243. https://doi.org/10.1016/S0041-1345(96)00482-4
•de Melo GAN, Fonseca JP, Farinha TO, Pinho RJ, Damião MJ, Grespan R, da Silva EL, Bersani-Amado CA, Cuman RKN (2012). Anti-inflammatory activity of *Salvia officinalis* L. J. Med. Plants Res. 6(35): 4934-4939.
•De Woskin RD, Sweeney LM, Teeguarden JG, Sams R, Vandenberg J (2013). Comparison of 7740 PBTK model and biomarker based estimates of the internal dosimetry of acryla mide. Food Chem. Toxicol. 58: 506-521. https://doi.org/10.1016/j.fct.2013.05.008
•Devaraj S, Singh U, Jialal I (2009). The evolving role of C-reactive protein in atherothrombosis. Clin. Chem. 55: 229–238. https://doi.org/10.1373/clinchem.2008.108886
•Devi N, Sarma J, Das M (2014). Blood compatible hydrogel composed of starch, 2-acry lamido-2-met hylpropane sulfonic acid and acryl amide. Int. J. Latest Res. Sci. Technol. 3(4): 205-210.
•Durling NE, Catchpole OJ (2007). Extraction of phenolics and essential oil from dried sage (*Salvia officinalis*) using ethanol water mixtures. Food Chem. 101: 1417-1424. https://doi.org/10.1016/j.foodchem.2006.03.050
•Elsayed ASI, Bayomy MFF, Azab AE (2016). Effect of acute and chronic treatment of cyclosporine A on liver and kidney functions in rats. J. Appl. Pharma. Sci. 6(03): 116-119. https://doi.org/10.7324/JAPS.2016.60320
•Ezejiofor A, Udowelle NA, Orisakwe OE (2016). Nephroprotective and antioxidant effect of aqueous leaf extract of Costus Aferker gawl on cyclosporin-A (CsA) induced nephrotoxicity. Clin. Phytosci. 2 (11): 1197-1199.
•Gala´n AI, Mun˜oz ME, Jime´nez R (1999). S-adenosylmethionine protects against cyclosporine A-induced alterations in rat liver plasma membrane fluidity and functions. J. Pharmacol. Exp. Ther. 290: 774 –781.
•Gateva S, Jovtchev G, Stankov A (2015). Salvia extract can decrease DNA damage induced by zeocin. Int. J. Pharma. Med. Biol. Sci. 4(1): 1-10.
•Guillermo AD, Doscoteaux A (2014). Macrophages cytokines involvement in immunity and infectious diseases. Front. Immuonol. 5: 491-501.
•Hajzadeh MAR, Rajaei Z, Ghamami G, Tamiz A (2011). The effect of *Salvia officinalis* leaf extract on blood glucose in streptozotocin – diabetic rats. Pharmacol. Online. 1: 213-220.
•Hamidpour M, Hamidpour R, Hamidpour S, Shahlari M (2014). Chemistry, pharmacology, and medicinal property of Sage (Salvia) to prevent and cure illnesses such as obesity, diabetes, depression, dementia, lupus, autism, heart disease, and cancer. J. Tradit. Complem. Med. 4(2): 82-88. https://doi.org/10.4103/2225-4110.130373
•Hammad AY, Osman ME, Abdelgadir WS (2013). Effects of acrylamide toxicity on growth performance and serobiochemisty of Wistar rats. British J. Pharmacol. Toxicol. 4(4): 163-168.
•Hanudle M, Jüppner H, Salusky IB (2016). Fibroblast growth 23: fueling the fire. Kidney Int. 90: 928-930. https://doi.org/10.1016/j.kint.2016.08.013
•Harborne JB (1984). Phytochemical methods a guide to modern techniques of plant analysis. Chapman and Hill, London. Pp. 5.
•Haroun SA, Al-Shehin AM (2001). Cytogenetic effect of *Kochia indica* extract on *Vicii faba* L. Cytologia. 66: 377-378. https://doi.org/10.1508/cytologia.66.373
•Hegde S, Pahne J, Smola-Hess S (2004). Novel immunosppressive properties of interlukin-6 in dendritic cells: inhibition of NF-Kappa B binding activity and CCR7 exoression. "Federation of American Societies for Experimental Biology" J. 18 (12): 1439-1441.
•Herna´ndez-Saavedra D, Pe´rez-Ramı´rez IF, Ramos-Go´mez M, Mendoza-Dı´az S, Loarca-Pin˜a G, Reynoso-Camacho R (2015). Phytochemical characterization and effect of *Calendula officinalis*, *Hypericum perforatum*, and *Salvia officinalis* infusions on obesity associated cardiovascular risk. Med. Chem. Res. 25(1): 163-172. https://doi.org/10.1007/s00044-015-1454-1
•Horthov E, Srančkov A, Melušov ERM, Meluš V, Netriov J, Krajčovičov Z, Slameňov D, Pastorek M, Kozics K (2015). Enriching the drinking water of rats with extracts of *Salvia officinalis* and *Thymus vulgaris* increases their resistance to oxidative stress. Mutagenesis. 00: 1–9
•Indran M, Mahmood AA, Kuppusamy UR (2008). Protective effect of *Carica papaya* L. leaf extract against alcohol induced acute gastric damage and blood oxidative stress in rats. West Indian Med. J. 57(4): 133-137.
•Ivanov I (2008). Free radicals and cares for aging pets. Trakia J. Sci. 6(1): 152-154.
•Jin F, Lai LC, Dong JX, Ning L (2014). Immunotoxicity of Acrylamide in Female BALB/c mice. Biomed. Environ. Sci. 27(6): 401-409.
•Jin X, Coughlan M, Roberts J, Mehta R, Raju J (2016). Dietary acrylamide exposure in male F344 rats: Dataset of systemic oxidative stress and inflammation markers. Data Brief. 7: 460-467. https://doi.org/10.1016/j.dib.2016.02.024
•Jeon YJ, Kim YS (2011). Cyclosporine A inhibits albumin synthesis in Huh7 cells. Korean J. Int. Med. 26: 314-319. https://doi.org/10.3904/kjim.2011.26.3.314
•Jones MC, Power DA, Cunningham C, Stewart KN, Catto GRD (1988). Alloantibody and transferable suppressor activity induced by cyclosporine and blood transfusion in the rat. Transplantation, 46(5): 645-649. https://doi.org/10.1097/00007890-198811000-00003
•Kienhuis AS, Vitins AP, Pennings JL, Pronk TE, Speksnijder EN, Roodbergen M (2013). Cyclosporine A treated *in vitro* models induce cholestasis response through comparison of phenotyp e-directed gene expression analysis of *in vivo* Cyclosporine A-induced cholestasis. Toxicol, Lett. 221(3): 225–236. https://doi.org/10.1016/j.toxlet.2013.06.236
•Li J, Li D, Yang Y, Xu T, Li P, He D (2016). Acrylamide induces locomotor defects and degeneration of dopamine neurons in Caenorhabditis elegans. J. Appl. Toxicol. 36: 60-67. https://doi.org/10.1002/jat.3144
•Liping J, Jun C, Yu A, Chengyan G (2007). Genotoxicity of acrylamide in human hepatoma G2 (HepG2) cells. Toxicol. *In Vitro*. 21 (8): 1486–1492. https://doi.org/10.1016/j.tiv.2007.06.011
•LoPachin RM, Balaban CD, Ross JF (2003). Acrylamide axonopathy. Toxicol. Appl. Pharmacol. 188: 135-153. https://doi.org/10.1016/S0041-008X(02)00072-8
•López L, Arai K, Giménez E, Jiménez M, Pascuzo C, Rodríguez-Bonfante C, Bonfante-Cabarcas R (2006). C-reactive

protein and interleukin-6 serum levels increase as Chagas disease progresses towards cardiac failure. Rev. Esp. Cardiol. 59(1): 50-56. https://doi.org/10.1157/13083649

•Madhok R, Torley HI, Capell HAA (1991). Study of the longterm efficacy and toxicity of cyclosporine A in rheumatoid arthritis. Rheumatol. 18: 1485.

•Mahmood SAF, Amin KAM, Salih SFM (2015). Effect of acrylamide on liver and kidneys in Albino Wistar rats. Int. J. Curr. Microbiol. Appl. Sci. 4(5): 434-444.

•Manna F, Abed-Wahhab MA, Ahmed H, Park M H (2006). Protective role of *Panax ginseng* extract standardized with ginsenoside Rg3 against acrylamide-induced neurotoxicity in rats. J. Appl. Toxicol. 26 (3): 198-206. https://doi.org/10.1002/jat.1128

•Mathieu P, Lemieux I, Despre´s JP (2010). Obesity, inflammation and cardiovascular risk. Clin. Pharmacol. Therapeut. 87: 407–416. https://doi.org/10.1038/clpt.2009.311

•Mostafavi-Pour Z, Khademi F, Zal F, Sardarian AR, Amini F (2013). *In vitro* analysis of CsA-induced hepatotoxicity in HepG2 cell line: oxidative stress and α2 and β1 integrin subunits expression. Hepat. Mon. 13(8): e11447. https://doi.org/10.5812/hepatmon.11447

•Mukul Das MH, Prahlad KS (1982). Effect of acrylamide on brain and hepatic mixed-function oxidases and glutathione-transferase in rats. Toxicol. Appl. Pharmacol. 66(3): 420-426. https://doi.org/10.1016/0041-008X(82)90308-8

•Musso T, Espinoza-Delgado I, Pulkki K, Gusella GL, Longo DL, Varesio L (1992). IL-2 induces IL-6 production in human monocytes. J. Immunol. 148: 795-800.

•Naruszewicz M, Zapolska-Downar D, Kos´mider A, Nowicka G, Kozłowska-Wojciechowska M, Vikstroöm AS, To¨rnqvist M (2009). Chronic intake of potato chips in humans increases the production of reactive oxygen radicals by leukocytes and increases plasma C-reactive protein: a pilot study. Am. J. Clin. Nutr. 89: 773–777. https://doi.org/10.3945/ajcn.2008.26647

•Nixon BJ, Stanger SJ, Nixon B, Roman SD (2012). Chronic exposure to acrylamide induces DNA damage in male germ cells of mice. Toxicol. Sci. 129(1): 135-145. https://doi.org/10.1093/toxsci/kfs178

•Nixon BJ, Katen AL, Stanger SJ, Schjenke JR, Nixon B, Roman SD (2014). Mouse spermatocytes express CYP2E1 and respond to acrylamide exposure. J. Pone. 9(5): 1-11. https://doi.org/10.1371/journal.pone.0094904

•Oboh G, Henle T (2009). Antioxidant and inhibitory effects of aqueous of *Salvia officinalis* leaves on pro oxidant- induced lipid peroxidation in brain and liver *in vitro*. Med. Food. 12: 77 -84. https://doi.org/10.1089/jmf.2008.0007

•Oduola T, Adeniyi FAA, Ogunyemi EO, Bello IS, Idowu TO, Subair HG (2007). Toxicity studies on an unripe *Carica papaya* aqueous extract: biochemical and haematological effects in Wistar albino rats. J. Med. Plants Res. 1(1): 001-004.

•Osman NN, Abd El-Azime A Sh (2013). *Salvia officinalis* L. (sage) ameliorates radiation-induced oxidative brain damage in rats. Arab J. Nuclear Sci. Appl. 46 (1): 297 – 304.

•Parsai A, Eidi M, Sadeghipourm A (2014). Hepatoprotective effect of sage (*Salvia officinalis* L.) leaves hydro – methanolic extract against aspergillus parasiticus aflatoxine – induced liver damage in male rats. Bull. Pharma. Res. 4(3): 129-132.

•Pepys MB, Hirschfield GM (2003). C-reactive protein: Acritical update. J. Clin. Invest. 111: 1805-1812. https://doi.org/10.1172/JCI200318921

•Petrova M, Nikolova M, Dimitrova L, Zayova E (2015). Micropropagation and evaluation of flavonoid content and antioxidant activity of *Salvia officinalis* L. Gene. Plant Physiol. 5(1): 48–60.

•Pop AV, Tofană M, Socaci SA, Nagy M, Fărcas A, Borş MD, Salanta L, Feier D, Vărva L (2014). Comparative study regarding the chemical composition of essential oils of some salvia species. Hop. Med. Plants. 1(2): 79-91.

•Rezzani R (2004). Cyclosporine A and adverse effects on organs: histochemical studies. Prog. Histochem. Cytochem. 39(2): 85–128. https://doi.org/10.1016/j.proghi.2004.04.001

•Rodrigues MR, Kanazawa LK, das Neves TL, da Silva CF, Horst H, Pizzolatti MG, Santos AR, Baggio CH, Werner MF (2012). Antinociceptive and anti-inflammatory potential of extract and isolated compounds from the leaves of *Salvia officinalis* in mice. J. Ethnopharmacol. 139 (2): 519-526. https://doi.org/10.1016/j.jep.2011.11.042

•Russo A, Formisano C, Rigano D, Senatore F, Delfine S, Cardile V, Rosselli S, Bruno M (2013). Chemical composition and anticancer activity of essential oils of Mediterranean sage (*Salvia officinalis* L.) grown in different environmental conditions. Food Chem. Toxicol. 55: 42–47. https://doi.org/10.1016/j.fct.2012.12.036

•Ryzner M, Takáčová J, Čobanová K, Plachá I, Katarína Venglovská K, Faix Š (2013). Effect of dietary *Salvia officinalis* essential oil and sodium selenite supplementation on antioxidative status and blood phagocytic activity in broiler chickens. Acta Vet. Brno. 82: 043–048.

•Sabeeh RI (2016). Protective role of selenium and melatonin on some parameters related to oxidative stress and metabolic syndrome induce by acrylamide in male rats. MSc. Thesis, College of Veterinary Medicine, University of Baghdad.

•Sadek KM (2012). Antioxidant and immunostimulant effect of *Carica papaya* linn. aqueous extract in Acrylamide intoxicated rats. Acta. Inform. Med. 20(3): 180-185. https://doi.org/10.5455/aim.2012.20.180-185

•Savage JRK (1975). Classification and relationship of induced chromosomal structural change. J. Med. Genet. 12: 103-112.

•Scheller J, Chalaris A, Schmid-Arras D, John S (2011). The pro-infalammatort and anti-inflammatory properties of cytokine interlukin-6. Biochim. Biophys. Acta. 1813: 878-888. https://doi.org/10.1016/j.bbamcr.2011.01.034

•Song FU, Ying YI, Chao Yang XI, Wei LI, Zhang ZG, Li C, Lan ZX (2013). Acrylamide alters cytoskeletal protein level in rat serum. Biomed. Environ. Sci. 26(11): 926-929.

•Snedecor GW, Cochran WG (1973). Statistical methods. 6th ed. The Iowa State University Press. Pp. 238-248.

•Srivastava SP, Das M, Seth PK (1983). Enhancement of lipid peroxidation in rat liver on acute exposure to acrylamide and styrene a consequence of glutathione depletion. Chem. Obiol. Interact. 45(3): 373-380. https://doi.org/10.1016/0009-2797(83)90083-2

•Svensson U, Holst E, Sundler R (1995). Cyclosporine-sensitive expression of cytokine mRNA in mouse macrophages responding to bacteria. Mol. Immunol. 32: 157–165. https://doi.org/10.1016/0161-5890(94)00107-C

•Szabóová R, Lauková A, Chrastinová L', Simonová M, Strompfová V, Haviarová M, Plachá I, Faix Š, Vasilková Z, Chrenková M, Rafay J (2008). Experimental application of sage in rabbit husbandry. Acta Vet. Brno. 77: 581-588. https://doi.org/10.2754/avb200877040581

•Szalowska E, Stoopen G, Groot MJ, Hendriksen PJ, Peijnenburg AA (2013). Treatment of mouse liver slices with cholestatic

hepatotoxicants results in down-regulation of Fxr and its target genes. BMC Med. Genet. 6(1): 39. https://doi.org/10.1186/1755-8794-6-39

•Tabl GA, Massoud AA, Karolin K, Barakat KK, Elwy AM, Elghazaly MM (2014). Modulation of toxicological effect of Carrageenan-induced paw odema using sage oil from *Salvia officinalis* as anti-inflammatory and antioxidant drug. J. Drug Res. Egypt. 35(1): 43-56.

•Tenore GC, Ciampaglia R, Arnold NA, Piozzi F, Napolitano F, Rigano D, Senatore F (2011). Antimicrobial and antioxidant properties of the essential oil of *Salvia lanigera* from Cyprus. Food Chem. Toxicol. 49(1): 238-243. https://doi.org/10.1016/j.fct.2010.10.022

•Tilg H, Norberg J, Vogel W, Lugcr TA, Herold M, Aultlky WC Margrester K, Huber R (1992). Circulating serum levels of interlcukin- 6 and C-reactive protein after liver transplantation. Transplantation. 54: 142. https://doi.org/10.1097/00007890-199207000-00025

•Tirkey N, Kaur G, Vij G, Chopra, K (2005). Curcumin, a diferuloylmethane, attenuates cyclosporine-induced renal dysfunction and oxidative stress in rat kidneys. BMC Pharmacol. 5: 15 https://doi.org/10.1186/1471-2210-5-2

•Totani N, Yawata M, Ojiri Y, Fujioka Y (2007). Effects of trace acrylamide intake in Wistar rats. J. Oleo. Sci. 56: 501–506. https://doi.org/10.5650/jos.56.501

•Tülay AC, Ozlem SA (2010). Evaluation of cytotoxicity of Inula viscosa extracts with *Allium cepa* test. J Biomed Biotechnol. Volume (2010), 1-7. Article ID 189252, 8 pages http://dx.doi.org/10.1155/2010/189252.

•Uz E, Uz B, Kaya A, Akdeniz D, Ruzgaresen NB, Uz E, Turgut F, Bayrak R, Akcay A (2012). Protective effect of erdosteine on cyclosporine induced chronic nephrotoxicity in rats. Nephro-Urol. Mon. 3(4): 280–284.

•Vanuffelen BE, Van Der Zee J, De Koster BM, Vansteveninck J, Elferink JG (1998). Intracellular but not extracellular conversion of nitroxyl anion into nitric oxide leads to stimulation of human neutrophil migration. Biochem. J. 330(2): 719-722. https://doi.org/10.1042/bj3300719

•Venkataswamy M, Sumanm B, Lakshmamma VN, Venkatasubbaiah K, Thyaga Raju K (2015). Acrylamide interaction with Neuron – Glutathione – Stransferases (GSTs): molecular docking study in developing chick embryo. World J. Pharm. Pharma. Sci. 4(07): 1024-1032.

•Wagdy KBK, Faiza A (2013). Effects of *Salvia officinalis* extract and its nano-encapsulated form on methylmercury induced neurotoxic-stress in male rats. World Appl. Sci. J. 24 (7): 826-837.

•Waters V, Sokol S, Reddy B, Soong G, Chun J, Prince A (2005). The effect of Cyclosporine A on airway cell Proinflammatory signaling and pneumonia. Am. J. Resp. Cell. Mol. Biol. 33: 138–144. https://doi.org/10.1165/rcmb.2005-0005OC

•Weber K, Osborn M (1982). Microtubules and intermediate filament networks in cells viewed by immunofluorescence microscopy. In: Cell surface reviews (eds. G. Post, G.I. Nicolson). Biomedical Press, Amsterdam, New York.

•Weber BK, Jones MC, Hillis G, Catto GH, Catto GRD, Macleod AM (1991). Effect of cyclosporin A on immunoglobulin class in patients receiving blood transfusions. Kidney Inter. 39: 328-332. https://doi.org/10.1038/ki.1991.41

•Wielgus K, Luwanska A, Szalata M, Mielcarek S, Gryszczynska A, Lipinski D, Slomski R (2011). Phytochemical estimation of Sage (*Salvia officinalis* L.) cultivated in vitro-flavonoids and phenolic acids. Acta Fytotech. Zootech. 14: 8–11.

•Wolf A, Trendelenburg CF, Dı´ez-Ferna´ndez C, Prieto P, Houy S, Trommer WE, Cordier A (1997). Cyclosporine A-induced oxidative stress in rat hepatocytes. J. Pharmacol. Exp. Ther. 280: 1328 –1334.

•Wu X, Zhang W, Hayes Jr D, Mansour HM (2013). Physicochemical characterization and aerosol dispersion performance of organic solution advanced spray-dried cyclosporine A multifunctional particles for dry powder inhalation aerosol delivery. Int. J. NanoMed. 8: 1269-1283.

•Xing XL, Lu Y, Qiu HL (2016). Effect of cyclosporin A particles of varying diameters on gastric cancer cell apoptosis. Genet. Mol. Res. 15 (2): 2-8. https://doi.org/10.4238/gmr.15028085

•Zamorano-Ponce E, Morales C, Ramos D, Sepulveda C, Cares S, Rivera P, Fernandez J, Carballo MA (2006). Anti-genotoxic effect of Aloysia triphyllainfusion against acrylamide-induced DNA damage as shown by the comet assay technique. Mut. Res. 603: 145–150. https://doi.org/10.1016/j.mrgentox.2005.11.009

•Zhang X, Cao J, Jiang L, Geng C, Zhong L (2009). Protective effect of hydroxytyrosol against acrylamide-induced cytotoxicity and DNA damage in HepG2 cells. Mut. Res. 664: 64–68. https://doi.org/10.1016/j.mrfmmm.2009.02.013

•Zhang L, Gavin T, Barber DS, LoPachin RM (2011). Role of the Nrf2-ARE pathway in acrylamide neurotoxicity. Toxicol. Lett. 10, 205(1): 1–7.

•Zhang L, Wang E, Chen F, Yan H, Yuan Y (2013). Potential protective effects of oral administration of allicin on acrylamide-induced toxicity in male mice. Food Funct. 4: 1229–1236. https://doi.org/10.1039/c3fo60057b