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ORIGINAL ARTICLE

The analysis of the protective feature of *Nigella sativa* in reducing Carbimazole toxicity including liver and kidney parameters on Albino male rats

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ABSTRACT

Objective: Carbimazole is widespread drug utilized for treating hyperthyroidism but ,carbimazole usage was associated with adverse on some organs. Also, carbimazole overdose has been linked to nephritis in rats, while , *Nigella sativa* a medical plant has many antioxidant effects against liver and kidney" toxicity" so , the aim of study was to explore the protective effect of *Nigella sativa* against carbimazole-induced hepatic and renal toxicity in rats.

Methods: The experiment was done on 24 male albino rats in Karbala University /animal house of Pharmacy College for two months period, this work considered the agreement of the animal rights in the college. The rats were divided into four groups, the first group is control which represented healthy animals , the second group is carbimazole group was drenched orally with 1.6 mg/kg/day of carbimazole , the third group was drenched orally with 4ml/kg of *Nigella* for three days in a week plus l.6 mg/kg/day of carbimazole and last group was drenched 4ml/kg of Nigella for three days per week. The samples of Blood were collected for lab analysis including the liver and kidney functions and tissues were underwent for histopathological evaluation.

Results: The study demonstrated significant effect of *Nigella* in reducing the toxicity of "carbimazole" in both biochemical parameters for liver and kidney ("ALT, AST, ALP, Urea, Creatinine") and in histological section as mentioned below in results.

Conclusion: From the results we concluded that *Nigella sativa* may have protective effect against "carbimazole toxicity".

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INTRODUCTION

Hyperthyroidism was considered as cub-clinical case when there were slightly elevation in peripheral thyroid hormones, but still with normal range. Hypothalamus-pituitary axis sensitive to elevation of thyroid hormones and ultimately a reverse feedback mechanism will outcome trough decreasing thyrothrophic hormone (TSH), indeed subclinical hyperthyroidism may be symptomatic or asymptomatic[1]. In the United States they found hyperthyroidism prevalence is about 1.2% including 0.7% subclinical conditions and 0.5% explicit

cases. The ultimate current causes include Graves' disease, toxic variant of multinodular thyroid disease and toxic adenoma[2].

Carbimazole is widespread drug utilized for treating hyperthyroidism, it is 3-carbethoxy methimazole derivative. After treatment using this drug for 2,4 and 6 weeks durations there was significant reduction in thyroid-stimulating hormone and thyrotropin-binding inhibitory immunoglobulins[3,4]. Furthermore, usage of carbimazole was associated with adverse effect on certain organs. Ali *et al* [5] announced that carbimazole resulted in necrosis of renal tubules of rats. Marzuela *et al* [6] pointed that carbimazole was ambidextrous in producing cholestatic hepatitis and acute pancreatitis[7], necrotizing glomerulonephritis and pulmonary hemorrhage all were related to carbimazole usage[8]. Heidari *et al* [9] pointed that carbimazole usage caused a granulocytosis and severe cholestatic jaundice with hepatotoxicity. It induce intracanalicular cholestatic jaundice and little mononuclear cell infiltrate within the portal triades through blastogenic response of patient lymphocytes involving antigen stimulating immune reaction particularly cholestasis created by sensitized lymphocytes[10].

Carbimazole toxicity is associated with kidney impairment shown as different glomerular defects such as necrotizing glomerulonephritis[11], lupus nephritis[12] or vasculitis[13].

The flowering plant *Nigella sativa* belongs to Ranunculaceae family which is annual herbaceous plant is currently called black seed or black cumin[14] *Nigella sativa* has been vastly used in Middle east, Far East, South east Asia, Europe and India as spicy flavors and inbred therapy for many sicknesses as infections, asthma, vertigo, headache, obesity, hypertension, cough influenza, vertigo and fever[15]. It was stated that *Nigella sativa* presents plentiful pharmacological consequences like antioxidants[16], anti- inflammatory[17] antimicrobial[18] antidiabetic[19], antihypertensive[20], Neuroprotective and anticarcinogenic[21]. The properties of *Nigella sativa* of main chemical components are alkaloid, 2 % essential oil, 37% fixed oil, proteins, vitamins, carbohydrates and minerals[22].

The aims of the study: The aim of the present study is to evaluate the "protective effect" of *Nigella sativa* in the toxicity of carbimazole in albino rats.

MATERIALS AND METHODS

Animals and chemicals

Between March 2016 and 2017, 35consecutive breast cancer patients who underwent mastectomy at Basrah general Hospital were registered. All patients were women with ages ranging from 21 to 62 years. None of the patients received neo adjuvant chemotherapy. Paraffin-embedded material of 35 breast cancer patients, including 24 IDC and 11DCIS, was used for histological analysis, diagnosed at the Institute for Pathology at Basrah general Hospital (Table 1). Tumour typing and staging were performed according to the classification of the International Union against Cancer[15], TNM classification, tumor diameter and hormone receptor (estrogen receptor (ER), progesterone receptor (PR) HER2 and human epidermal growth factor receptor-2) were obtained from pathology reports.

Biochemical measurements

For biochemical study "Aspartate aminotransferase and Alanine aminotransferase" were colorimetrically identified in regard to early research[25] as well as alkaline phosphatase[26], creatinine[27] and urea[28] were examined.

Histopathological preparations

The treated animals were scarified after two months by cervical decapitation, rats were dissected immediately after decapitation then the liver and kidney were removed and fixed with 10% formalin. After this step they were soaked in an ascending series of alcohol for dehydration, then clearance was done by xylene double changes and firmed in molted paraffin wax , microtome (HM 355S Automatic Microtome) was used to slice wax in little thickness of five microns followed by mounting on proper slides. then staining with Ehrlichs heamatoxylin and counterstained with eosin ,at last the pathologist examined the slides in Olympus microscope at (400x)[29].

Statistical analysis

Data were expressed as mean ± SE. Differences between control and other experimental groups were tested for statistical significance using SPSS version 20 one-way analysis of variances (ANOVA) (post hoc. and LSD) . $P \leq 0.05$.

RESULTS

Biochemical results

Table 1 Show the effect of *Nigella sativa* against carbimazole toxicity on liver and kidney function of male rats, there were significant reducing in ALT, AST, ALP, Urea, Creatinine values 49.66, 77.50, 119.66, 46.83, 0.21 ; respectivilly, as compared with carbimazole group 84.33, 104.16, 152, 67, 0.37 , while in *Nigella* group the results were near to control group 44.33, 75.66, 108.50, 42.66, 0.24.

Table1: **The effect of *Nigella sativa* against carbimazole toxicity on liver and kidney function of male rats.**

Parameters / Groups	ALT U/L	AST U/L	ALP U/L	Urea Mg/dl	Creatinine Mg/dl
Control group(1)	41.83±2.38^a	67.50±0.92^a	100.33±0.76^a	38.33±0.80^a	0.23±.009^a
Carbimazole group(2)	84.33±2.60^b	104.16±2.35^b	152.00±2.90^b	67.00±2.0^b	0.37±.006^b
(Carbimazole +nigella) group(3)	49.66±1.49^c	77.50±2.60^c	119.66±0.55^c	46.83±1.4^c	0.21±.008^c
Nigella sativa group 4	42.33±1.58^a	69.66±1.40^a	103.50±1.52^a	40.66±0.8^a	0.22±.003^a

Different small letter means significant changing.-a, b, c means significant difference between control, carbimazole ,carbimazole +nigella and nigella groups.
$P \leq 0.05$.

Histological results

1- Control group : In case of liver section in this group was noticed normal central vein with hepatocytes arranged radially around it .While in kidney the section showed the normal glomeruli and tubules .

2- Carbimazole group: The liver section showed significant congestion, focal degeneration and single

cell coagulated necrosis .while in kidney there was well defined tubular epithelial cell necrosis, glomerular congestion, with focal mild chronic inflammatory cellular aggregates. (tubules affected rather than glomeruli).

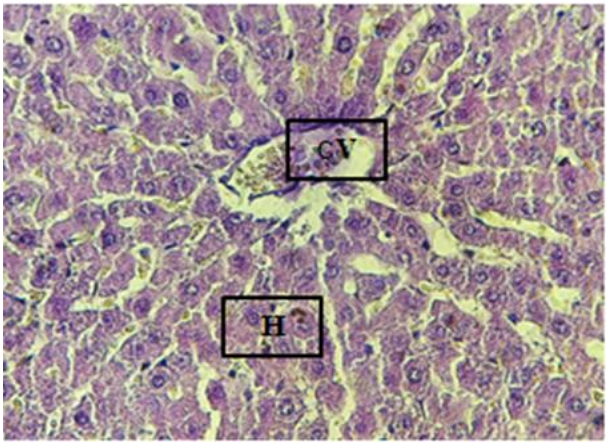

Figure 1 A: **Cross section of liver in control group showed CV: central vein , H: hepatocytes. (400X, H&E stain)**

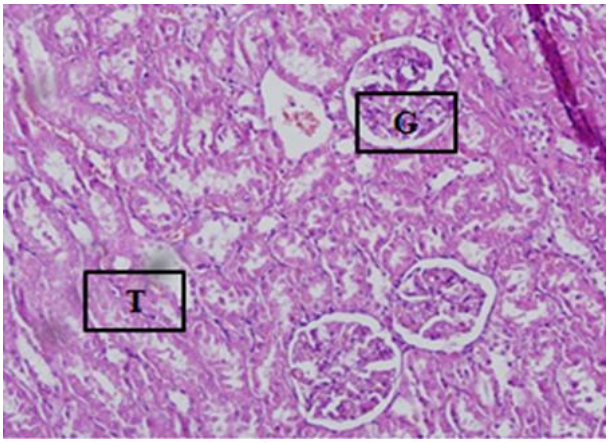

Figure 1 B: **Cross section of kidney in control group showed G: normal structure of glomeruli , T: tubules. (400X, H&E stain)**

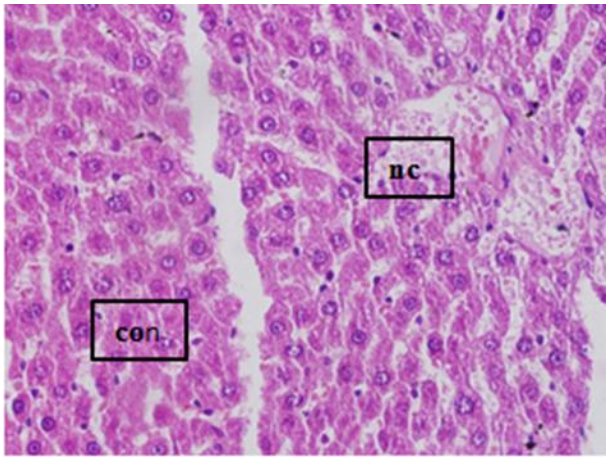

Figure 2 A: **Cross section of liver in carbimazole group showed nc: necrosis , co: congestive (400X, H&E stain)**

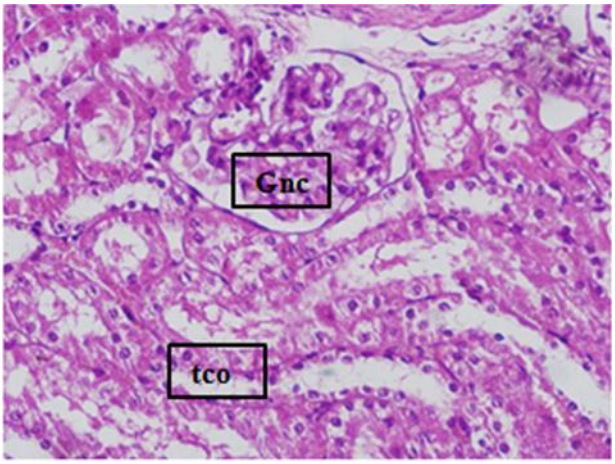

Figure 2 B: **Cross section of kidney in carbimazole group showed Gnc: glomeruli necrosis, tco: tubuler congestion(400X, H&E stain)**

3- Carbimazole +*Nigella* group: In case of liver: regular hepatocytic plates and lobular architecture with still seen are the necrosis and little degeneration. While in kidney section: partial response to treatment by decrease congestion, absence of inflammation although still necrosis seen.

4- *Nigella* group: in liver section: No remarkable pathology seen in liver tissue. in the case of kidney :preserved tubular and glomerular architecture with intraluminal proteincous secretion, no necrosis or degeneration.

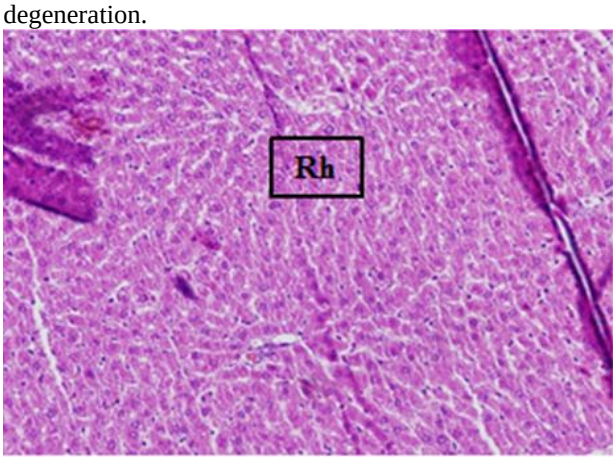

Figure 3 A: **cross section of liver in carbimazole+nigella group showed Rh: regular hepatocytes (400X, H&E stain)**

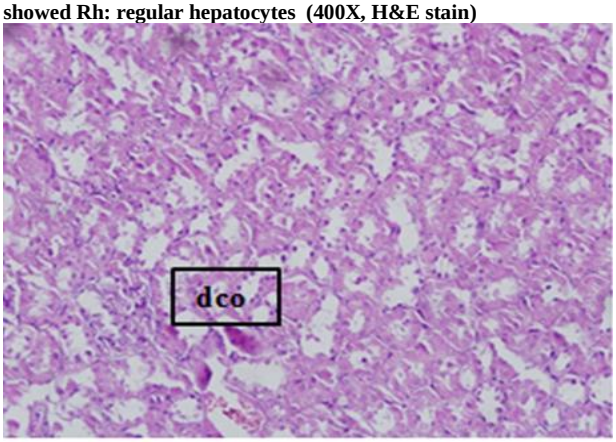

Figure 3 B: **Cross section of kidney in carbimazole+nigella group showed dco: decrease congestion with still necrosis (400X,H&E stain)**

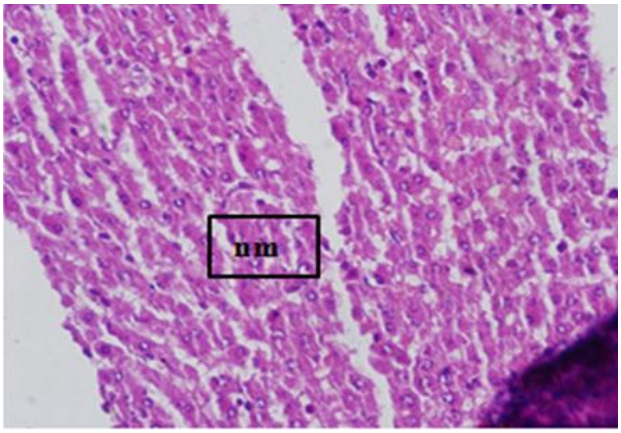

Figure 4 A: **Cross section of liver in Nigella group showed nm: No mark able pathology (400X, H&E stain)**

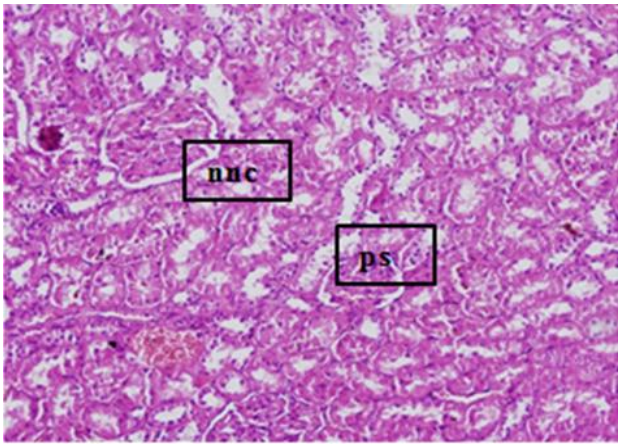

Figure 4 B: **Cross section of kidney in Nigella group showed nnc: no necrosis, ps: intraluminal protein secrsion (400X, H&E stain)**

DISCUSSION

Carbimazole overdose causes negative impacts on liver and renal tissues through enzyme activities of rats, so from the following results there were significant elevation in (ALT, AST, ALP) values, this may be as a result of hepatocellular damage by the toxicity of carbimazole which led to diffuse these enzymes from damaged liver cells to blood stream, this opinion agreed with[30]. Also, Ajayi and Akhigbe reported an increment in aminotransferases following achieving hypothyroidism by carbimazole treating rats[31], They appended that lytic process in hepatocytes was resulted from carbimazole usage. Moreover Kota *et al* [32] reported that "carbimazole induced cholestatic hepatitis in Grave disease". so this results gave an evidence for hepatorenal toxicity of rats by carbimazole. The elevation in creatinen level might be accounted to the disorder of kidney function and considered as a good indicator of renal toxicity of carbimazole. The path histological results for hepatorenal exhibits the damage of hepatocytes cells as necrosis and degeneration, inflammation ,furthermore losing spacing , likewise necrosis in glomeruli and damage in renal tubules that is agreed with previous studies[33,34].

On the other hand *Nigella sativa* showed "protective effect" in reducing and preventing the damage which induced by carbimazole, so from the table there are significant effect of *Nigella* in shifting hepatorenal parameters ALT, AST, ALP and creatinen urea to normal value, that is clear argument of the protective impacts of this antioxidant item in repairing the damaged cells that is agreed with Salama *et al* and El Daly[35,36], who depicted that the administration of *Nigella sativa* concomitant with alternative drenched carbimazole decreased the rise of serum creatinen and urea concentrations, this is a good evidence on *Nigella sativa* as anti-inflammatory which was return to its inhibit effects on cyclooxygenase and lipoxygenase enzymes in line with Salem ML[37]. Moreover studies showed that *Nigella* has protective effect in removing the toxin from cells or reducing its amount by repairing liver and kidney tissues and reducing degeneration and inflammation in cells and vessels . From these results we conclude the protective effect of *Nigella sativa* against carbimazole toxicity.

Conclusions

From our results we conclude that *Nigella sativa* may have anti-inflammatory and protective effect against Carbimazole toxicity.

Recommendation

We recommended deeply studies on the effect of *Nigella sativa* on antioxidant parameters.

REFERENCES

1. Cooper D.S. and Biondi B. "Subclinical thyroid disease". Lancet. 2012; 379(9821):1142–54. DOI:10.1016/S0140-6736(11)60276-6
2. Singer P.A., Cooper D.S.and Levy E.G. "American Thyroid Association Standards of Care Committee. Treatment guidelines for patients with hyperthyroidism and hypothyroidism". JAMA.1995; 273:808-812.
3. Abbassy A.A., Kamel S.S., Assaad S.N. and Eid W.E. "Ultrasonographic and doppler study of the thyroid gland in Graves' disease before and after treatment with antithyroid drugs". Endocrinol. Pract. 1997; 3(4): 225-230. DOI:10.4158/EP.3.4.225 .
4. Frénais R., Burgaud S. and Horspool L.J. "Pharmacokinetics of controlled release carbimazole tablets support once daily dosing in cats". J. Vet. Pharmacol. Ther. 2008; 31(3): 213-219. DOI:10.1111/j.1365-2885.2008.00949.x .
5. Ali B.H., Bashir A.A. and Tanira M.O. "The effect of thyroxine or carbimazole treatment on gentamicin nephrotoxicity in rats". Hum. Exp. Toxicol.1995; 14(1): 13-17. DOI:10.1177/096032719501400103 .
6. Marazuela M., Sánchez de Paco G., Jiménez I., Carraro R., Fernández- Herrera J. and Pajares J.M. "Acute pancreatitis, hepatic cholestasis and erythema nodosum induced by carbimazole treatment for Graves' disease". Endocr. J. 2002; 49(3): 315-318.
7. Zaidi T.M., Khan A.A., Hasan B.M. and Faruq A.N. "Carbimazole induced thyroid histopathy in Albino rats during development". J. Anat. Soc. India. 2004; 53(2): 14-17.
8. Calañas-Continente A., Espinosa M., Manzano-García G., Santamaría R., Lopez-Rubio F. and Aljama P. "Necrotizing glomerulonephritis and pulmonary hemorrhage associated with

carbimazole therapy". Thyroid. 2005; 15(3): 286-288. DOI:10.1089/thy.2005.15.286 .
9. Heidari R., Babaei H. and Eghbal M.A. "Ameliorative effects of taurine against methimazole-induced cytotoxicity in isolated rat hepatocytes". Sci. Pharm. 2012; 80(4): 987-99. DOI:10.3797/scipharm.1205-16 .
10. Arab D.M., Malatjalian D.A. and Rittmaster R.S. "Severe cholestatic jaundice in uncomplicated hyperthyroidism treated with methimazole". J. Clin. Endocrinol. Metab.1995; 80:1083. DOI:10.1210/jcem.80.4.7714072 .
11. Yu F., Chen M., Gao Y., Wang S.X., Zou W.Z. and Zhao M.H. "Clinical and pathological features of renal involvement in propylthiouracil-associated ANCA-positive vasculitis". Am. J. Kidney Dis. 2007;49(5):607–14. DOI:10.1053/j.ajkd.2007.01.021.
12. Wang L.C., Tsai W.Y., Yang Y.H. and Chiang B.L. "Methimazole-induced lupus erythematosus: A case report". J. Microbiol. Immunol. Infect. 2003; 36(4): 278–81.
13. Calanas-Continente A., Espinosa M., Manzano-Garcia G., Santamaria R., Lopez-Rubio F. and Aljama P. "Necrotizing glomerulonephritis and pulmonary hemorrhage associated with carbimazole therapy". Thyroid. 2005; 15(3): 286–8. DOI:10.1089/thy.2005.15.286 .
14. Butt M.S. and Sultan M.T. "*Nigella sativa*: reduces the risk of various maladies". Crit. Rev. Food Sci. Nutr. 2010; 50(7): 654–665. DOI:10.1080/10408390902768797 .
15. Khazdair M.R. "The Protective Effects of Nigella sativa and Its Constituents on Induced Neurotoxicity". J. Toxicol. 2015; 2015:1–7. DOI:10.1155/2015/841823 .
16. Ashraf S.S., Rao M.V., Kaneez F.S., Qadri S., Al-Marzouqi A.H., Chandranath I.S. and Adem A. "*Nigella sativa* extract as a potent antioxidant for petrochemical-induced oxidative stress". J. Chromatogr. Sci. 2011; 49(4): 321–326.
17. Ahmad A., Husain A., Mujeeb M., Alam Khan S., Najmi A.K., Siddique N.A, Damanhouri Z.A. and Anwar F. "A review on therapeutic potential of Nigella sativa: A miracle herb". Asian Pac J Trop Biomed. 2013; 3(5): 337–352.
18. Morsi N.M. "Antimicrobial effect of crude extracts of Nigella sativa on multiple antibiotics-resistant bacteria". Acta. Microbiol. Pol. 2000; 49(1): 63–74.
19. Ali mohammadi S., Hobbenaghi R., Javanbakht J., Kheradmand D., Mortezaee R., Tavakoli M., Khadivar F. and Akbari H. "Protective and antidiabetic effects of extract from *Nigella sativa* on blood glucose concentrations against streptozotocin (STZ)-induced diabetic in rats: an experimental study with histopathological evaluation". Diagn. Pathol. 2013; 8:137.
20. Fallah Huseini H., Amini M., Mohtashami R., Ghamarchehre M.E., Sadeqhi Z., Kianbakht S. and Fallah Huseini A. "Blood pressure lowering effect of *Nigella sativa* L. seed oil in healthy volunteers: a randomized, double-blind, placebo-controlled clinical trial". Phytother. Res. 2013; 27(12): 1849–1853. DOI:10.1002/ptr.4944 .
21. Khan A., Chen H.C., Tania M. and Zhang D.Z. "Anticancer Activities of Nigella sativa (Black Cumin)". Afr. J. Tradit. Complement Altern. Med. 2011; 8(5): 226–232. DOI:10.4314/ajtcam.v8i5S.10 .
22. Al-Naqeeb G., Maznah I. and Al-Zubairi A.S. "Fatty acid profile, α-tocopherol content and total antioxidant activity of oil extracted from Nigella sativa seeds". Int. J Pharmacol. 2009 ; 5(4): 244–250. DOI: 10.3923/ijp.2009.244.250 .
23. Paget G.E and Barnes J.M. "Toxicity tests. In: Laurence D.R., Bacharach A.L., editors. Evaluation of drug activities: pharmacometries". London and New York: Academic Press . 1964; p. 135-166.
24. Marwa A.A. and Khaled M.A.H. "Cardio protective effects of Nigella sativa oil on lead induced cardio toxicity: Anti-inflammatory and antioxidant mechanism". Journal of physiology and pathology. 2013; 4(5): 72-80. DOI: 10.5897/JPAP2013.0083.
25. Reitman S., Frankel S. "A colorimetric method for the determination of serum glutamic oxalacetic and glutamic pyruvic transaminases". Am. J. Clin. Pathol. 1957; 28(1): 56-63.
26. King P.R.N. and King E.J. "Estimation of plasma phosphatase by determination of hydrolyzed phenol with amino antipyrine". J. Clin. Path.1954; 7: 322-326.
27. Tietz, N.W., Prude E.L. and Sirgard-Anderson O. "In: Tietz Textbook of Clinical Chemistry". ed. Burtis C.A. and Ashwood, E.R. 1994; 1354– 1374. W. B. Saunders Company, London.
28. Kaplan A. "Urea nitrogen and urinary ammonia. In: Standard Method of Clinical Chemistry". ed. Meites S.1965; 245 – 256. Academic Press Inc., New York.1965.
29. Banchroft J.D., Stevens A. and Turner D.R. "Theory and practice of histological techniques". 4th ed. 1996.Churchil living stone, New York, London, San Francisco ،Tokyo.
30. Sherlock S. "Disease of the liver and biliary system". 8th ed.1981. Oxford: Blackwell Scientific Publication.
31. Ajayi A.F. and Akhigbe R.E. "Implication of altered thyroid state on liver function" .Thyroid Res Pract. 2012; 9(3): 84-87.
32. Kota S.K., Meher L.K., Kota S.K., Jammula S. and Modi K.D. "Carbimazole induced cholestatic hepatitis in Graves disease". Indian journal of Endocrinology and metabolism. 2013; 17(2): 326-328.
33. Lunzer M., Huang S.N., Ginsburg J., Ahmed M. and Sherlock S. "Jaundice due to carbimazole". Gut. 1975 ; 16(11): 913-917.
34. Blom H., Stolk J., Schreuder H.B. and von Blomberg-van der Flier M. "A case of carbimazole-induced intrahepaticcholestasis. An immune-mediated reaction?". Arch. Intern. Med. 1985; 145(8): 1513-1515.
35. El Daly E.S. "Protective effect of cysteine and vitamin E, Crocus sativus and Nigella sativa extracts on cisplatin-induced toxicity in rats". J. Islamic Acad. Sci. 1998; 53(2): 87–93.
36. Salama R.H.M., Abd-El-Hameed N.A., Abd-El-Ghaffar S.K.H., Mohammed Z.T. and Ghandour N.M.A. "Nephroprotective Effect of Nigella sativa and Matricaria chamomilla in Cisplatin Induced Renal Injury". Int. J. Clin. Med. 2011; 2(3): 185–195. DOI: 10.4236/ijcm.2011.23031 .
37. Salem M.L. "Immunomodulatory and therapeutic properties of the Nigella sativa L. seeds". Int. Immunopharmacol. 2005; 5(13-14): 1749-70.