التغيرات الكيموحيوية والنسيجية التى تحدث في ذكور الجرذان البيضاء المعالجة عن طريق الفم بمركب الكاريزوبرودول

ليلى عبدالقوى

يستخدم مركب الكاريزوبرودول (سومادريل)^{R} بشكل واسع في ارتخاء العضلات والهيكل العظمى، وكمسكن، ومناح كدواء.

الهدف من العمل: هو التعرف على التغيرات الكيموحيوية والنسيجية فى الكبد بعد تناول السومادريل عن طريق الفم فى ذكور الجرذان البيضاء، حيث لوحظ إساءة استخدام هذا الدواء بين الشباب فى سن المراهقة فى الأونة الأخيرة كبديل غير مكلف للمخدرات غير المشروعة.

طريقة العمل: تم حقن ذكور الجرذان البيضاء بجرعات من مركب الكاريزوبرودول (80 مج، 120جم/100مج من وزن الجسم) المشابه للجرعة العلاجية والجرعات فوق العلاجية فى الإنسان) مذابة فى 2 مللى من زيت الذرة لمدة 15و30و45 يوما، وأعقب مجموعة الحقن لمدة 45 يوما فترة من الانسحاب لمدة 15 يوما (W15) .

وتم قياس إنزيمات وظائف الكبد، ومستويات الجلوتاثيون في الدم (اختزال وأكسدة). وبالإضافة إلى ذلك، تم تقيم إنزيم الباراوكسيناز (paraoxinase)، سيتوكروم ب450 (CYT P450) ، انترلوكن 6 (IL-6)، وحالة الأكسدة / مضادات الأكسدة والتى تم تقييمها فى الكبد عن طريق قياس مستويات المالون دى الدهيد (MDA malondialdehyde)، سوبر أوكسيد ديسميوتاز(SOD)، الجلوتاثيون المختزل (GR)، الكاتلاز (CAT)، والجلوتاثيون بيروكسيديز(GPX). وعلاوة على ذلك، تم فحص التغيرات النسيجية للكبد.

النتائج: أظهرت النتائج ارتفاع كبير فى مصل إنزيمات الكبد(ALT، AST، ALP، γGT)فى ذكور الجرذان المعالجة مقابل المجموعة الضابطة، وقد انخفض بشكل ملحوظ تركيز الجلوتاثيون المختزل (GSH) في جرعات 15و30و45 يوما وكذلك فى مجموعه فتره الانسحاب (W15). فى حين لوحظ زيادة كبيرة فى مستوى الأكسدة، وكذلك انخفض GSSG / GSH فى كل المجموعات بالمقارنة بالمجموعة الضابطة.

كما أظهرت النتائج زيادة كبيرة في محتوى المالون داى الدهيد (MDA) وانخفاض كبير في نشاط GR، مع إعاقة واضحة فى النشاط من قبل الكاتلاز. أيضا، تحقق إعاقة واضحة فى إنزيم سوبر أوكسيد ديسميوتاز فى ذكور الفئران المعالجة بالسومادريل مقابل المجموعات الضابطة. وقد انخفض بشكل ملحوظ تركيز GSH فى D15، D45 D30 وW15 ، فى حين حدثت زيادة كبيرة في مستوى الأكسدة، وكذلك انخفض GSSG / GSH فى D15، D30، D45 و W15 بالمقارنة بالمجموعة الضابطة. كما انخفض بشكل ملحوظ نشاط مصل إنزيم الباراوكسيناز وسيتوكروم ب 400. وعلاوة على ذلك كشف الفحص النسيجى لأنسجة الكبد فى الجرذان وجود تغيرات ملحوظة بشكل كبير.

الاستنتاجات: هذه التغييرات الضارة تعطى إنذارا للحذر عند استخدام مثل هذه المجموعة من العقاقير، واتخاذ القرارات بشأن تنظيم استخدام مركب الكاريزوبرودول لما له من مخاطر صحية.

69- Lakshimie B.; Tilak jc., Adhikari s.; Devasagayam TPS.; Janardhanan KK., Inhibition of lipid peroxidation induced by Gamma-raddiation and AAPH in rat liver and brain mitochondria by mushrooms. Curr. Sci., 88, 2005, pp. 484-488.

70- Kregel K Cand Zhang H., An integrated view of oxidative stress in aging: basic mechanisms, functional effects, and pathologicalconsiderations. Am J Physiol Regul Integr Comp Physiol, 292, 2007, pp. 18–36.

71- Neila Fathallah, Michele Zamy, Raoudha Slim, Olivier Fain, Houssem Hmouda, Kamel Bouraoui, Chaker Ben Salem, Michel Biour, Acute Pancreatitis in the Course of Meprobamate Poisoning. JOP. J Pancreas .,12 (4), 2011, pp. 404-406.

72- Johnkennedy N, Adamma E, Austin A, Chukwunyere NNE., Alterations in biochemical parameters of Wister rats administered with sulfadoxine and pyrimethamine (FansidarR). Al Ameen J. Med.Sci. 3 (4), 2010, pp. 317-321.

73- Rajesh MG, Latha MS., Preliminary evaluation of the antihepatotoxic activity of Kamilari, a polyherbal formulation. J Ethnopharmacol.; 91 (1), 2004, pp. 99-104.

74- Mohamed Marzouk, Amany A. Sayed and Amel M. Soliman, Hepatoprotective and antioxidant effects of *Cichoriumendivia* L. leaves extract against acetaminophen ,Journal of Medicine and Medical Sciences , 2, 2011, pp. 1273-1279.

And also:

- Bhadauria Mand Nirala SK., Reversal of acetaminophen induced subchronic hepatorenal injury by propolis extract in rats. Environ Toxicol Pharmacol. , 27 (1), 2009, pp. 17-25.
- Yuan HD, Jin GZ, Piao GC., Hepatoprotective effects of an active part from Artemisia sacrorum Ledeb. against acetaminophen-induced toxicity in mice. J Ethnopharmacol. 2010 Feb 3; 127 (2), 2010, pp. 528-33.

75- Premila A., Oxidative stress in paracetamol induced pathogenesis: (I) Renal damage.Indian J. Biochem. Biophy., 42, 2005, pp. 59-62.

76- Jaeschke H, McGill MR and Ramachandran A., (2012): Oxidant stress, mitochondria, and cell death mechanisms in drug-induced liver injury: Lessons learned from acetaminophen hepatotoxicity. Drug Metab Rev.; 44 (1), 2012, pp. 88-106.

77- Rajasekaran A and Periyasamy M., (2012): Hepatoprotective effect of ethanolic extract of Trichosanthes lobata on paracetamol-induced liver toxicity in rats., Chin Med., 18; 7 (1), 2012, p. 12.

activity is due to an alteration in the PON1's free sulfhydryl groups. Atherosclerosis, 185, 2006, pp. 191–200.

61- Padurariu M, Ciobica A, Dobrin I, Stefanescu C., Evaluation of antioxidant enzymes activities and lipid peroxidation in schizophrenic patients treated with typical and atypical antipsychotics. Neurosci Lett.; 479 (3), 2010, pp. 317-20.

62- Nazia Uzmal, B. Santhosh Kumarand and Syeda Anees, Red wine ameliorates CCl4 – induced acute liver injury in rats. AJBS., 1 (1), 2011, pp. 1-7.
And also:
- Memduh Kermanl, Nilgun Senol, Oxidative stress in hippocampus induced by 900 MHz electromagnetic field emitting mobile phone: Protection by melatonin. Biomedical Research 2012; 23 (1). 2012, pp. 147-151.

63- Hfaiedh N, Murat J-C, Elfeki A., A combination of ascorbic acid and α-tocopherol or a combination of Mg and Zn are both able to reduce the adverse effects of lindane-poisoning on rat brain and liver. Journal of Trace Elements in Medicine and Biology, 26 (4), 2012, pp. 273-8

64- Hussien HM, Abdou HM, Yousef MI.(2013): Cypermethrin induced damage in genomic DNA and histopathological changes in brain and haematotoxicitin rats: The protective effect of sesame oil.; Brain Res Bull., 92, 2013, pp. 76-83.
And also:
- Brzóska M; Rogalska J; Malgorzata; RoszczenkoA; Jurczuk M., Effect of zinc supplementation on glutathione peroxidase activity and selenium concentration in the serum, liver and kidney of rats chronically exposed to cadmium. Journal of Trace Elements in Medicine and Biology; 26 (1), 2012, pp. 46–52.

65- Duntas LH., The evolving role of selenium in the treatment of Graves' disease and Ophthalmopathy. Journal of Thyroid Research, 2012, pp. 736161-6.

66- Sankar P, Telang AG, Manimaran A., Protective effect of curcumin on cypermethrin-induced oxidative stress in Wistar rats. Experimental and Toxicologic Pathology; 64,2012.pp.487– 493.

67- Sun Y, Ma A, Li Y, Han X, Wang Q, Liang H., (2012):Vitamin E supplementation protects erythrocyte membranes from oxidative stress in healthy Chinese middle-aged and elderly people. Nutrition research 2012; 32: 328 – 334.

68- Ishita C, Biswas K, Bandyopathyay U and Banerjee RK., Trmeric and euramin: Biological actions and medical applications. Current Science, 37, 2004, pp. 44-53.

paracetamol-induced hepatotoxicity in rats. Rev. bras. farmacogn., 21 (1), 2011, pp. 133-138.

54- Jyotsna AP; Arun jp; Ajit VS; Satish DK and Sanjay PG., Effect of methomyl on the Phenobarbital and Benzo(a) Pyrene Induced Hepatic Microsomal Mixed Function Oxidase System in Rats. AJMS, 4 (2), 2011, pp. 144-151.

55- Deniz E and Şukru B., Effect of some analgesics on Paraoxonase-1 purified from human serum. Journal of Enzyme Inhibition and Medicinal Chemistry, 24 (4), 2009, pp. 1034-1039.

56- Bramness JG, Skurtveit S, Faskel Grung M, Molven A, Morland j., op. cit.

And also:

- Sorin E. Leucuta and Laurian Vlase, Pharmacokinetics and Metabolic Drug Interactions. Current Clinical Pharmacology, 1, 2006, pp. 5-205.
- Vidyavati S Koppisetti and Nikhil Chandra, Influence of Alcohol and Smoking on Drug Action: A Step for better utilization of drugs. J Chem Pharm Res., 3 (1), 2011, pp. 242-248.

57 - Parola M and Robino G., Oxidative stress-related molecules and liver fibrosis. J Hepatol., 35, 2001, pp. 297-306.

And also:

- FerréN, Marsillach J, Camps J, Mackness B, Mackness M, Riu F, Coll B, Tous M, Joven J., Paraoxonase-1 is associated with oxidative stress, fibrosis and FAS expression in chronic liver diseases. Journal of Hepatology, 45, 2006, pp. 51-59.
- Krzystek-Korpacka, M., Boehm, D., Matusiewicz, M., Diakowska, D., Grabowski, K., Gamian, A., Paraoxonase 1 (PON1) status in gastroesophageal malignancies and associated araneoplastic syndromes, connection with inflammation. Clinical Biochemistry 41, 2008, pp. 804–811.
- Marsillach, J., Aragonès, G., Beltrán, R., Caballeria, J., Pedro-Botet, J., Morcillo-Suárez, C., Navarro, A., Joven, J., Camps, J., The measurement of the lactonase activity of paraoxonase-1 in the clinical evaluation of patients with chronic liver impairment. Clinical Biochemistry, 42, 2009, pp. 91-98.

58- Khaled Gamal El-Deen Abdel-Wahhab, Yasser Ashry Khadrawy and Fathia Abd Elwahid Mannaa, Aged garlic extract enhances paraoxonase 1 activity and suppress oxidative stress in CCl_4 intoxicated rats .Comunicata Scientiae, 3(1), 2012, pp. 55-63.

59- Josse D, Bartels C, Lockridge D, Masson P., PON1 structure. In: Costa LG, Furlong CE, editors. Paraoxonase (PON1) in health and disease: basic and clinical aspects. Norwell (MA): Kluwer Academic Publishers, 2002, PP. 27–52.

60- Jaouad L, Guise C, Berrougui H, Cloutier M, Isabelle M, Fulop T, PavetteH and Khalil A., Age-related decreased in high-density lipoproteins antioxidant

43- Liu J, Wang Y, Cui J, Xing L, Shen H, Wu S, Lian H, Wang J, Yan Xand Zhang X., Ochratoxin A induces oxidative DNA damage and G1 phase arrest in human peripheral blood mononuclear cells in vitro. Toxicol Lett., 211 (2), 2012, 164-71.

44- Hamm ML, Crowley KA, Ghio M, Lindell MA, Mcfadden EJ, Silberg JSandWeaver AM., Biochemical Investigations into the Mutagenic Potential of 8-Oxo-2'-deoxyguanosine Using Nucleotide Analogues. Chem Res Toxicol., 25 (11), 2012, pp. 2577-88

45- Delogu G, Moretti S, Marcellini S, Antonucci A, Tellan G, Marandola M, Signore Mand Famularo G., Pancuronium bromide, a non-depolarizing muscle relaxant which promotes apoptosis of blood lymphocytes in vitro. Acta Anaesthesiol Scand., 47 (9), 2003, pp. 1138-44.

46- Kiso K, Ueno S, Fukuda M, Ichi I, Kobayashi K, Sakai T, Fukui K, Kojo S., The role of Kupffer cells in carbon tetrachloride intoxication in mice. Biol Pharm Bull., 35 (6), 2012, pp. 980-3.

47- Hooshyar Honarm and, Mohammad Abdollahi, Arezoo Ahmadi, Mohammad R Javadi et al., (2012): Biomarkers and outcome in febrile critically ill adults. DARU Journal of Pharmaceutical Sciences, 20, 12, 2012, pp. 2008-2231.

48- Rajagopal V Sekhar, Sanjeet G Patel, Anuradha P Guthikonda, *et al.*, Deficient synthesis of glutathione underlies oxidative stress in aging and can be corrected by dietary cysteine and glycine supplementation. Am J Clin Nutr., 94 (3), 2011, pp. 847-853.

49- Liu, RM and Gaston Pravia KA., Oxidative stress and glutathione in TGF-β-mediated fibrogenesis. Free Radical Biology and Medicine, 48 (1), 2010, pp. 1-15.

50- Boelsterli UA and Lim PL., op.cit.

51- Françoise Auchère, Renata Santos, Sara Planamente, Emmanuel Lesuisse and Jean-Michel Camadro, Glutathione-dependent redox status of frataxin-deficient cells in a yeast model of Friedreich's ataxia .Hum. Mol. Genet., 17 (18), 2008, pp. 2790-2802.

52- Tony KL Kiang, Xiao Wei Teng, Jayakumar Surendradoss, Stoyan Karagiozov, Frank S. Abbott, Thomas KH Chang", Glutathione depletion by valproic acid in sandwich-cultured rat hepatocytes: Role of biotransformation and temporal relationship with onset of toxicity. Toxicology and Applied Pharmacology, 252 (3), 2011, pp. 318-324.

53- Patel K N; Gupta Gajendra; Goyal M and Nagori b P., Assessment of hepatoprotective effect of Tecomella undulata (Sm.) Seem., Bignoniaceae, on

31- Bergmeyer HV and Bernt E., Method for aspartate and alanine aminotransferase. In: Methods of enzymatic analysis. Bergmeyer (ed), Vol. 2, Verlag Chemie, Weinheim, Academic Press, New York and London,1974, p. 735.

32- Tietz NW., Fundamentals of Clinical Chemistry, W.B. Saunders co., 1982, p. 603.

33- Szasz GA., Determination of serum gamma glutamyl transferase. Clin Chem.; 15, 1969, p. 124.

34- Botsoglou NA., Rapid sensitive and specific thiobarbituric acid method for measuring lipid peroxidation in animal tissue, food and feedstuff samples. J. Agric. Food Chem., 42,1994,pp.1931-1937.

35- Sinha AK., **Colorimetric assay of catalase.** Anal Biochem.; 47 (2), 1972, pp. 389-94.

36- Paglia DE and Valentine WN., Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase. J Lab Clin Med.; 70, 1967, pp. 158–169.

37- Bompart GJ; Prévot DS and Bascands JL., Rapid automated analysis of glutathione reductase, peroxidase, and S-transferase activity: application to cisplatin-induced toxicity. Clin Biochem, 23 (6), 1990, pp. 501–504.

38- McCord JM and Fridovich I., Superoxide dismutase. An enzymic function for erythrocuprein (hemocuprein) J Biol Chem., 244 ,1969, pp. 6049–6055.

39- Omura T and Sato R., The carbon monoxide-binding pigment of liver microsomes: I. Evidence for its hemoprotein nature . JBio Chem., 239, 1964, 2370-2378.

40- Liang KW, Lee WJ, Lee IT, Lee WL, Lin SY, Hsu SL, Wan CJ, Yu CY, Tsai IC, Fu CP, Ting CT and Sheu WH., Persistent elevation of paraoxonase-1 specific enzyme activity after weight reduction in obese non-diabetic men with metabolic syndrome. Clin Chim Acta., 18, 412 (19-20), 2011, pp. 1835-41.

41- Humason GL., Preparation and staining of histological specimen. In: "Animal tissue techniques" 3rd ed., W. H. Freeman and Co., Sanfrancisco., 1972.

42- Lee JE, Park JH, Shin ICand Koh HC., (2012): Reactive oxygen species regulated mitochondria-mediated apoptosis in PC12 cells exposed to chlorpyrifos. Toxicol Appl Pharmacol., 263 (2), 2012, pp. 148-62.

And also:

- Chen AF, Chen DD, Daiber A, Faraci FM, Li H, Rembold CM and Laher I., Free radical biology of the cardiovascular system. Clin Sci., 123 (2), 2012, pp. 73-91.

22- Moling O, Cairon E, Rimenti G, Rizza F, Pristerá, Mian P., (Severe hepatotoxicity after therapeutic doses of acetaminophen. Clin Ther.,; 28, 2006, pp. 755-60.

And also:

- Dart RC and Bailey E., Does therapeutic use of acetaminophen cause acute liver failure? Pharmacotherapy; 27, 2007, pp. 1219-30.

23- Snel J and Lorist MM., "Effects of caffeine on sleep and cognition". Progress in Brain Research, 190, 2011, pp. 105–17.

24- Verbeeck RK., Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction". Eur J Clin Pharmacol., 64 (12), 2008, pp. 1147–61.

And also:

- Arnaud MJ., "Pharmacokinetics and metabolism of natural methylxanthines in animal and man". Handbook of Experimental Pharmacology, 200 (200),2011,pp. 33–91

25- Lara DR., "Caffeine, mental health, and psychiatric disorders". J. Alzheimers Dis.,2010,pp.S239–S248.

26- Bramness JG., op.cit.

27- Flaten, M.A.; Simonsen, T.; Zahlsen, K., Aamo, T.; Sager, G.; Olsen, H., Stimulant and Relaxant Drugs Combined with Stimulant and Relaxant Information: A Study of Active Placebo. Psychopharmacology (Berl).,176(3-4),2004,pp.426-434.

And also:

- Serfer, G.T.; Wheeler, W. J.; Sacks, H. J., Randomized, Double-Blind Trial of Carisoprodol 250 mg Compared with Placebo and Carisoprodol 350 mg for the Treatment of Low Back Spasm. Curr. Med. Res. Opin., 26 (1), 2010, pp. 91-99.
- Zacny JP, Paice JAand Coalson DW., Subjective and psychomotor effects of carisoprodol in combination with oxycodone in healthy volunteers. Drug Alcohol Depend.; 120 (1-3), 2012, pp. 229-32.

28- Paget GE and Barnes JM., Evaluation of drug activities and phamacometries. Editors: RR Laurence and Bacharach AL, Academic Press, London; (1), 1964, pp. 135-166.

29- Houssiau, F A; Bukasa, K; Sindic, C J; Damme, J V and Snick, J V., (1988): Elevated levels of the 26K human hybridoma growth factor (interleukin 6) in cerebrospinal fluid of patients with acute infection of the central nervous system. Clin Exp Immunol.; 71(2), 1988, pp. 320–323.

30- Jayatilleke E and Shaw S., A high performance liquid chromatographic assay for reduced and oxidized glutathione in biological samples. Anal Biochem, 214 (2), 1993, pp. 452-457.

15- Gonzalez , L. A; Gatch, M.B;Forster, M. J; Dillon, G. H., op. cit.

16- Bramness JG, Skurtveit S, Faskel Grung M, Molven A, Morland j., Blood Carisoprodol: meprobamate concentration ratios and CYP2C19 genotypes in carisoprodol – drugged drivers: decreased metabolic capacity in heterozygous CYP2 C19: 1/CYP2 C19* 2 subjects? Pharmacoenetics, 13 (7), 2003, 383-8.

And also:

- Downey, D.; Simons, K.; Ota, K.; Kerrigan, S., op.cit.
- Wang G, Huynh K, Barhate R, Rodrigues W, Moore C, Coulter C, Vincent M, Soares J., Validation of a new homogeneous immunoassay for the detection of carisoprodol in urine. J Anal Toxicol., 35 (2), 2011 ,pp. 108-12.
- Alvarez, J. C.; Duverneuil, C.; Zouaoui, K.; Abe, E.; Charlier, P.; de la Grandmaison, G.L.; Grassin-Delyle, S., Evaluation of the first immunoassay for the semi-quantitative measurement of meprobamate in human whole blood or plasma using biochip array technology. Clin Chim Acta., 18, 413(1-2), 2012, pp. 273-7.

17- Blicharski, T.; Burdan, F.; Małkiewicz, J.; Piechota, G., Blockade of reticular formation activity due to carisoprodol maternal administration, and its effects on rat skeleton development. Ann Univ Mariae Curie Sklodowska Med., 57(1), 2002, PP. 143-9.

And also:

- Høiseth G, Karinen R, Sørlid HK, Bramness JG., The effect of scheduling and withdrawal of carisoprodol on prevalence of intoxications with the drug.Basic Clin Pharmacol Toxicol. 2009 Nov; 105 (5), pp. 345-9.

18- McIntyre IM, Sherrard J, Lucas J., Postmortem carisoprodol and meprobamate concentrations in blood and liver: lack of significant redistribution., J Anal Toxicol.; 36 (3), 2012, 177-81.

19- Prescott LF., Paracetamol, alcohol and the liver. British J Pharmacol., 49, 2000, pp. 291-301.

And also:

- Gyamlani GG and Parikh CR., Acetaminophen toxicity; Suicidal vs. accident. Critical Care, 6, 2002, pp. 155-159.

20- Lee SST, Buters JTM, Pineau T *et al.*, Role of CYP2E1 in hepatotoxiciy of acetaminophen, J Biolog Chem., 271, 2004, pp. 12063-12067.

21- Boelsterli UA and Lim PL (2007): Mitochondrial abnormalities-a link to idiosyncratic drug hepatotoxicity? Toxicol Appl Pharmacol., 220, 2007, pp. 92–107.

7- Bramness, JG., Buajordet, I. and Skurtveit, S., op. cit.

8- Bramness, JG; Buajordet, I and Skurtveit, S., op. cit.

9- Gonzalez, L. A; Gatch, M. B; Forster, M. J; Dillon, G. H., Abuse potential of Soma: the GABAG (A) Receptor as a target. Mol Cell Pharmacol., 1 (4), 2009, pp. 180-186.

10- Boothby, L.; Doering, P. and Halton, R., Carisoprodol a marginally effective skeletal muscle relaxant with serious abuse potential, journal of hospital pharmacy., 38, 2003, pp. 317-345.

And also:

- Guay, D. R, Are there alternatives to the use of quinine to treat nocturnal leg cramps? Consult Pharm. ,23(2),2008,141-56.
- Reeves, R.R. and Burke, RS., Carisoprodol: abuse potential and withdrawal syndrome. Curr Drug Abuse Rev., 3(1), 2010, pp. 33-8.

11- Musshoff, F, Stamer UM, Madea B Pharmacogenetics and forensic toxicology. Forensic Sci Int., 15, 203 (1-3), 2010, pp. 53-62.

12- Venugopal D, Deepak G, Murali N, Kumar KB, Sharma PS., A case report of carisoprodol dependence. Indian J Psychiatry., 42 (2), 2000, pp. 211-3.

And also:

- Heacock C.and Bauer MS., Tolerance and dependence risk with the use of carisoprodol. Am Fam Physician, 69(7), 2004, pp. 1622-3.
- Reeves RR, Hammer JS, Pendarvis RO., Is the frequency of carisoprodol withdrawal syndrome increasing? Pharmacotherapy., 27 (10), 2007, pp. 1462-6.
- Owens C, Pugmire B, Salness T, Culbertson V, Force R, Cady P, Steiner J., Abuse potential of carisoprodol: a retrospective review of Idaho Medicaid pharmacy and medical claims data. Clin Ther. 2007 Oct; 29 (10): 2222-5.
- Eleid MF, Krahn LE, Agrwal N, Goodman BP., Carisoprodol withdrawal after internet purchase. Neurologist, 16 (4), 2010, pp. 262-4.
- Gatch, M. B and Forster MJ. Behavioral and toxicological effects of propofol. Behav Pharmacol. 2011 Oct; 22 (7): 718-22.

13- Forrester MB., Ingestions of hydrocodone, carisoprodol, and alprazolam in combination reported to Texas poison centers. J Addict Dis., 30 (2), 2011, pp. 110-5.

And also:

- Zacny JP, Paice JAand Coalson DW., Characterizing the subjective and psychomotor effects of carisoprodol in healthy volunteers. Pharmacol Biochem Behav.; 100(1), 2011, pp. 138-43.

14- Ronning M., Drug consumption in Norway 1996-2000. Oslo: norweg an medicial Depot, 2001.

References

1- Patel RK, Patel MM, Patel MP, Kanzaria NR, Vaghela KRand Patel NJ., Hepatoprotective activity of Moringa oleifera Lam. Fruit on isolated rat hepatocytes. Phcog mag., 4, 2008, pp.118-23.

2- Bramness JG, Furu K, Skurtveit S, Engeland A., Effect of the market withdrawal of carisoprodol on use of other prescribed drugs with abuse potential. Clin Pharmacol Ther., 91(3), 2012, pp.438-41.

And also:

- Richards BL, Whittle SLand Buchbinder R., Muscle relaxants for pain management in rheumatoid arthritis. Cochrane Database Syst Rev.; 1, 2012, CD008922.

3- Kim, J. Y.; In, M. K.; Paeng, K. J.; Chung, B. C., Simultaneous determination of carisoprodol and meprobamate in human hair using solid-phase extraction and gas chromatography/mass spectrometry of the trimethylsilyl derivatives. Rapid Commun Mass Spectrom., 19(21), 2005, pp. 3056-3062.

And also:

- Downey, D.; Simons, K.; Ota, K.; Kerrigan, S., Quantitative Analysis of Carisoprodol and Meprobamate in Whole Blood Using Benzylcarbamate and Deuterated Meprobamate as Internal Standards. J. Anal. Toxicol., 33(5), 2009, pp. 278-82.
- Fass, J. A., Carisoprodol Legal Status and Patterns of Abuse. Ann. Pharmacother., 44 (12), 2010, pp. 1962-1967.

4- Bramness JG, Mørland J, Sørlid HK, Rudberg N, Jacobsen D., Carisoprodol intoxications and serotonergic features. Clin Toxicol (Phila)., 43(1), 2005, pp. 39-45.

And also:

- Bramness, JG; Buajordet, I and Skurtveit, S., The role of pharmacoepidemiological studies in the market withdrawal of carisoprodol (Somadril) in Europe, Norsk Epidemiologi, 18 (2), 2008, pp. 167-172.
- Reeves RRand Ladner ME., Carisoprodol withdrawal syndrome misdiagnosed as a psychotic disorder. Ann Clin Psychiatry., 20(3), 2008, pp. 173-174.
- Gatch MB and Forster MJ., Behavioral and toxicological effects of propofol. Behav Pharmacol.; 22(7), 2011, pp. 718-22.

5-Bramness JG., The pharmacokinetics, GYP2C19 pharmacogenetics and psychomotor impairment of the centrally acting muscle relaxant carisoprodol. Rikshospitalet, university hospital, university of Oslo, Norwegian Institute of Public Health, Division of Forensic Toxicology, Oslo, 2005, p.12- 13.

6- Bramness JG., op. cit.

diffuse into hepatocytes and trigger mitochondrial dysfunction and oxidant stress, which then induces MPT and necrotic cell death.

In conclusion, the results of this study demonstrate that carisoprodol compound has a potent hepatotoxic action and induced hepatic oxidative tissue damage in rats by increasing lipid peroxidation in the liver tissue, decreasing the level of antioxidant enzymes, increased liver function tests values and histological findings supported this conclusion. However, further investigations are required to identify, isolate, characterize and evaluate the active principal responsible for such hepatoxic activity.

Acknowledgment:
Thanks to the General Authority for Pharmaceutical Control for assistant and comment on the histological part of the present work.

treated rats, indicates APAP-induced liver impairment[74] in which hepatic markers were reportedly elevated. The elevated activities of serum AST, ALT and ALP in APAP induced liver injury indicative of cellular leakage and loss of functional integrity of cell membrane in liver[75].

Histological examination of liver tissue in carisoprodol comp. treated male rats significantly revealed marked changes included focal and confluent necrosis, portal tract inflammation and steotosis. These changes can be explained by Jaeschke *et al.*, 2012[76] which stated that mitochondria are the critical targets for drug toxicity, either directly or indirectly through the formation of reactive metabolites. The consequence of these modifications is generally a mitochondrial oxidant stress and nitrophil formation, which leads to structural alterations of proteins and mitochondrial DNA and, eventually, to the opening of mitochondrial membrane permeability transition (MPT) pores. MPT pore formation results in a collapse of mitochondrial membrane potential and cessation of adenosine triphosphate synthesis. In addition, the release of intermembrane proteins, such as apoptosis-inducing factor and endonuclease G, and their translocation to the nucleus, leads to nuclear DNA fragmentation. Together, these events trigger necrotic cell death.

Alternatively, the release of cytochrome C and other proapoptotic factors from mitochondria can promote caspase activation and apoptotic cell death. Moreover Rajasekaran and Periyasamy, 2012[77] explained the histopathological studies of rats administered paracetamol (one of active constituents of carisoprodol compound) which showed severe necrosis and disappearance of nuclei. This could be due to the formation of highly reactive metabolites (e.g. NAPQI), because of excessive administration of paracetamol.

These deleterious changes give an alarm to be aware in using such drug for a long time. It could be concluded that consumption of carisoprodol is contributing to health hazards and induced several hazards to liver by inducing an inflammatory response with the formation of reactive oxygen species by Kupffer cells and neutrophils. If not properly detoxified, these extracellularly generated oxidants can

The detoxification of ROS in liver involves the co-operative action of all intracellular antioxidant enzymes. Superoxide dismutase (SOD) is the first line of antioxidant enzymatic defense catalyzes the conversion of superoxide radicals to less toxic H2O2.Then catalase (CAT) metabolizes H2O2 to water .When this mechanism is saturated, the second line of antioxidant enzymatic defense mainly GPx that regulated by selenium availability is activated[65]. GPx are a family of selenium containing enzymes that responsible for detoxification of H2O2 and lipid peroxides at the membrane level into less reactive species using cellular GSH as substrate thus preventing the progressive formation of free radicals and provide the cell important protection aginst oxidative stress and LPO[66]. Many cells contain both CAT and GPx, while the liver GPx seems to be the major importance[67]. Moreover, Ishita *et al.*, 2004[68] found that the decreased activity of antioxidant enzyme in the liver after drug administration suggested the increased utilization and subsequent depletion of this antioxidant to counter the increased level of lipid peroxidation. Also the decrease in the activity of antioxidant enzymes might result from interaction of lipid peroxidation products with protein forming cross linkages that inactivate membrane bound enzymes[69]. Also, inactivation of enzymes may result also from the direct effect of drug that can break some chemical bonds in the protein molecule causing denaturation and inactivation of enzymes, in addition hydroxyl radicals (OH) and hydrogen peroxide (H2O2) cause oxidation of enzyme molecules and modification of their activities[70].

In the present study, the two doses of carisoprodol comp (21.6 and 43.2 mg) produced a significant increase in the activity of serum enzymes of liver functions (Tables 7and 8). Neila *et al.*, 2011[71] reported that, administration of meprobamate (the main metabolite of carisoprodol) increases the activity of liver function enzymes.

Serum AST, ALT, and ALP and γGT are the most sensitive biochemical markers employed in the diagnosis of hepatic dysfunction[72].

In liver injury the transport function of hepatocytes is disturbed, resulting in the leakage of plasma membrane[73]. The increase activities of AST, ALT, ALP, γGT level in serum of APAP

Moreover, the disulfide bond (cys-42 and cys- 353), in PON1 molecule, was found to be essential for its activity; while the free thiol (cys-284) was not; this suggesting that cys-284 is the active site responsible for the antioxidant property of PON1[59]. The highly reactive free radicals produced by carisoprodol, acetaminophen, caffeine metabolism can react with sulfhydryl groups, and it was stated that there is a close association between PON1 antioxidant activity and the number of –SH groups within PON1[60], therefore the reduction in PON1 antioxidant activity might be due to an alteration in nature and number of free thiol groups in its molecule.

In the present study, chronic administration of carisoprodol comp. 21.6 and 43.2 mg/100 g body weight of for 45 days resulted in a significant increase of lipid peroxidation (MDA) in liver tissue as indicating in Tables (5and6) which probably due to the interaction of the potent hydroxyl radicals (OH.) with the polyunsaturated fatty acids in the phospholipids portion of cell membrane initiating the lipid peroxidation chain reactions, produced greater tissue injury, therefore, liver MDA level revealed direct relationship between the severity of oxidation stress and drug toxicity[61]. The marked increase in MDA levels is likely to be a result of the inactivation of scavenger enzymes induced by reactive oxygen species (ROS)[62].

The data in Tables (5and 6) illustrated that the daily administration of carisoprodol at two doses for 45 days were significantly decreased the activity of the antioxidant defense enzymes (CAT, SOD, GPx and GR) in a dose dependant as compared with that of the normal rats. This depression of antioxidant enzyme activities reflects failure of the antioxidant defense mechanisms to overcome the influx of ROS induced by carisoprodol comp administration that leads to the accumulation of free radicals and facilitate the enhancement of LPO, which in turn increases the oxidative damage of the cell membrane and alteration in dynamic permeability of membranes due to peroxidation which is followed by the release of intracellular enzymes to the blood stream, so decreased the activity of liver antioxidant enzymes[63]. The current data are in accordance with previous results which reported a decreased activity of antioxidant enzymes in liver of treated rats[64].

(CYP3A4) convert paracetamol to a highly reactive intermediary metabolite, N-acetyl-*p*-benzoquinone imine (NAPQI). Under normal conditions, NAPQI is detoxified by conjugation with glutathione. In case of paracetamol toxicity, the sulfate and glucuronide pathways become saturated, and more paracetamol is shunted to the cytochrome P450 system to produce NAPQI. As a result, hepatocellular supplies of glutathione become exhausted and NAPQI is free to react with cellular membrane molecules, resulting in widespread hepatocytes damage and death, clinically leading to acute hepatic necrosis.

Also, the two doses of carisoprodol comp (21.6 and 43.2 mg) produced a significant decrease in the activity of cytp450 (Tables 3and4).Our results were in accordance with Jyotsna *et al.*, 2011[54] who stated that, decreased levels of cytochrome P450 may be due to inhibition of protein biosynthesis, methomyl (muscle relaxant) or its metabolite may inhibit the rate limiting enzymes of heme biosynthesis and decreased heme pool, which may results in the decreased activity of cytochrome P450 activity[55]. Moreover, carisoprodol is metabolized by the cytochrome P450 enzyme CYP2C19 through N-dealkylation to the active metabolite meprobamate which is deactivated the enzyme by forming mutated CYP2C19 alleles[56].

At the same time, significant change in the activity of paraoxinase (PON) enzyme noted at D**30** and D**45** post administration of 21.6 mg carisoprodol comp. /100g body weight (-16.98%, $P<0.01$ and -20.343% ,$P<0.01$) . After 15 days withdrawal followed the last dose (D45), the of paraoxinase enzyme level was found to be replenished back to that of the sham group (Table 3),while 43.2 mg/100g body weight, the withdrawal group (W**15**) was found to be significant (-17.122%, $p<0.01$). Our results can be explained as follows:

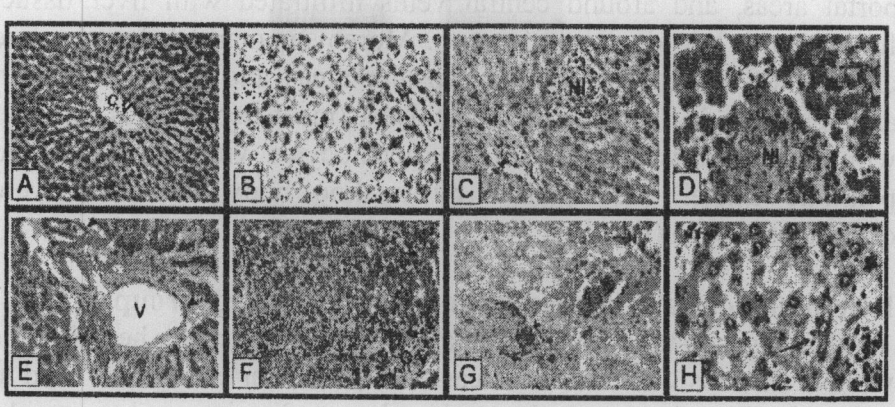
Liver plays the key role in the synthesis of serum PON1, and the gene expression has been observed only in the liver thus, the decrease in PON1 activity here may be due to the hepatic dysfunction induced by carisoprodol toxicity[57]. Also, As PON1 is known to be tightly bound with HDL-c, therefore, the decrease in PON1 activity could be a consequence of an altered synthesis and/or secretion of HDL-c.[58].

control group. Our results were in similarity with Delogu *et al.*, 2003[45] who stated that, drug administration produced tissue injury which induced inflammatory reactions in order to direct elements of the body defense and immune system to sites of injury, mediators including cytokines are released. Moreover, Kiso *et al.*,2012 [46] reported that drugs induced liver injury through two phases. The initial phase, involves the generation of reactive oxygen species. The second phase involves the oxidant-induced activation of Kupffer cells, which release various pro-inflammatory mediators such as interleukin-6 (IL-6). Hooshyar *et al.*, 2012[47] stated that since IL-6 is an anti-inflammatory cytokine, increased levels could be attributed to a compensatory reaction to hamper deleterious over inflammation by the toxins of the drug.

Tables (3, 4) recorded a significant reduction in the levels of reduced glutathione (GSH) and pronounced increased in its oxidized from (GSSG) compared to control group. The decrease of reduced glutathione may be attributed to oxidative stress which results from drug administration[48]. Also, the results are in line with that of Liu and Gaston, 2010[49], who stated that, cellular GSH concentration and the GSH/GSSG ratio are reduced markedly in response to oxidative stress and much pathological condition. Moreover, Boelsterli and Lim, 2007[50] reported that, paracetamol (one of carisoprodol compound constituents) is metabolically activated by cytochrome P450 enzymes to a reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI) that depletes GSH.

At the same time the decrease in NADPH, necessary for drug metabolism leads to a decrease in GSH level, as NADPH utilized to maintain GSH in the reduced form and increased the level of oxidized glutathione (GSSG)[51]. GSH can react with the end product of drug metabolism, therefore, another potential mechanism to explain the apparent loss of glutathione (GSH) in serum. (Tony *et al.,2011*)[52].

Moreover, Patel *et al*, 2011[53] reported that the PCM (paracetamol) is widely used analgesic-antipyretic agent and its large dose produces hepatic injury in man and experimental animals by depletion of glutathione and binding of toxic metabolite to vital proteins and enzymes. Cytochromes P450 2E1 (CYP2E1) and 3A4



Photograph of liver sections showing :

(A) Liver of normal control of rat hepatocytes radiating (H) in cord from the central vein(C.V) (H&E x 100)

(B) Liver section of treated rat apoptotic cells (►), kupffer cells prominent (K) and more or less normal liver cells (➔) (H&E x 200).

(C) Liver section of treated rat showing mild inflammatory cells in portal areas (⟶) and aggregation of inflammatory cells within liver lobules(NI), Kupffer cells (►) (H&E x 200).

(D) Liver section of treated rat showing aggregation of granulation tissue (NI) together with hyaline body formation(➔) and mild cytoplasmic vaculation (►) (H&E x 400).

(E) Liver section of treated rat showing mild inflammatory cells in portal areas (⟶) and mild thickening hyalinized body wall of portal vessels(►) and mild cytoplasmic vaculation (V) (H&E x 400).

(F) Liver section of treated rat showing aggregation of inflammatory cells within liver tissue (⟶►►), kupffer cells((►) and extravasated R.B.Cs (►) (H&E x 200).

(G) liver section of treated rat showing dilated congested blood vessels (⟶) and extravasated R.B.Cs (►) (H&E x 200)

(H) liver section of treated rat showing aggregation of inflammatory cells (necrotic areas) (►), inflammatory cells infiltrated within liver tissue (►►) and kupffer cells (►) (H&E x 400).

DISCUSSION:

Drug reactions may generate reactive oxygen species (ROS) as well as free radical, which caused damage of proteins, lipids and DNA[42]. Cells and organisms had developed several mechanisms to reduce toxicity induced by drug[43]. An in balance of these mechanisms increases the susceptibility to oxidative damage resulting in mutation, cancer, neurological diseases[44].

In the present study, results recorded in Tables (1, 2) showed that, the level of serum interlukin-6 (IL-6) was significantly increased ($p<0.001$) at dose 21.6 mg and 43.2 mg/100g body weight in D15, D30 and D45 of carisoprodol comp. treated rats in comparison with

In addition to, mild aggregated inflammatory cells in some portal areas, and around central veins infiltrated with liver tissue; furthermore, bile duct proliferation. Moreover, marked degenerative changes of hepatocytes in sub capsular areas and mild changes in another areas in the form of hepatolysis (most hepatocytes together with each other with demarcation), hepatocytes without nucleus and pyknotic nuclei accompanied by hyaline body formation were occasionally seen (Fig. F).

Histopathological Changes in the Liver of Treated Group (w15):
mild changes in the form of vaculated hepatocytes, many hepatic cells without nucleus were seen in areas. Also, vascular changes as mild to moderate dilated congested portal and central veins, and sinusoids, with extra vasated RBCs Moreover, some thickening and hyalinization wall of the portal veins were observed in areas (Fig. G). In addition to, bile ducts proliferation and perivascular aggregation of inflammatory cells and infiltrated within liver lobules, together with prominent kupffer cells and scattered minifoci of necrotic areas observed in some animals (Fig. H). Moderate improvement were seen in liver tissues in this group (W15) compared with group (A).

Histopathological Examination of the Liver of (15 days) Treated Animals:

The majority of hepatocytes in the liver of this group for (D15) treated animals, appeared normal in shape and structure, scattered individual numbers of apoptotic cells, beside. The pathological changes showed mild to moderate dilated, congested portal and central blood vessels with damaged wall (ruptured wall) of central veins, in most areas of this group seen (Fig. B). In addition to, mild to moderate aggregation of inflammatory reactions were seen in some portal areas and infiltrated within liver tissues observed in all animals. Moderate scattered foci of necro- inflammatory cells were noticed within liver tissues, accompanied by proliferated bile ducts, beside to, extra vasoted RBCs through liver tissues, and prominent kupffer cells. However, mild vascular degeneration changes of hepatocytes (coorsly cytoplasm) were also seen (Fig. C).

Histopatholoical Changes of Liver (D30) Treated Rats:

Mild to moderate changes in form of moderate inflammatory cells aggregated in most portal areas with individual numbers of eosinophilic hyaline bodies formation were seen scattered all over the parenchymal tissues and mild inflammatory cells infiltrated within liver lobules seen (Fig. D). Moreover mild scattered congested dilated portal blood vessels with mild thickened hyalinized walls. Beside extra vasated RBCs in many sites of sinusoids and mild to moderate aggregation of inflammatory cells reaction in portal areas seen (Fig. E). In addition, mild scattered focal areas of hepatocytes with pyknotic or karyolitic nuclei.

In other areas, there were mild to moderate swollen, vacuolated hepatocytes with coorsly cytoplasm and hyaline body was observed.

Histopatholoical Changes of Liver (D45) Treated Animals:

the changes in the form of moderate scattered congested dilated blood vasculature in areas and scattered haemorroghic areas beside moderate scattered apoptotic cells were also seen.

Table (8)
Effect of Chronic Administration of Carisoprodol Compound 43.2 mg /100g Body Weight on Serum ALT, AST, ALP and γ GT in Rats

Groups \ Parameter		ALT (IU/L)	AST (IU/L)	ALP (IU/L)	γGT (IU/L)
Control	Range	(34.11-60.91)	(91.71-181.4)	(163.91-211.84)	(25.81-33.41)
	Mean ±SD	45.39±7.6	134.71±6.32	193.74±7.2	28.94±2.6
D_{15}	Range	(40.77-71.39)	(181.8-229.1)	(241.81-317.8)	(37.84-53.81)
	Mean ±SD	63.51±3.6	204.13±16.9	284.7±11.45	46.4±5.6
	% change	39.89	51.35	46.95	60.37
	P<	0.01	0.001	0.001	0.001
D_{30}	Range	(60.39-95.11)	(181.9-284.81)	(258.3-319.7)	(35.93-53.11)
	Mean ± SD	75.84±8.94	243.53±20.6	298.3±23.8	48.39±8.11
	% change	67.09	80.78	98.46	67.21
	P<	0.001	0.001	0.001	0.001
D_{45}	Range	(69.41-114.34)	(319.4-421.8)	(277.9-334.8)	(43.81-55.87)
	Mean ±SD	91.79±11.84	378.8±16.6	308.3±15.4	49.3±4.2
	% change	102.23	181.19	59.130	70.35
	P<	0.001	0.001	0.001	0.001
W_{15}	Range	(60.81-91.54)	(186.1-284.9)	(201.8-358.9)	(37.91-55.84)
	Mean ±SD	69.11±10.91	218.61±14.41	297.8±11.9	45.3±7.0
	% change	52.25	62.28	53.71	56.53
	P<	0.001	0.001	0.001	0.001

P- Value <0.05 statistically significant.
D_{15}, D_{30}, D_{45} = time duration by days.
W_{15}= withdrawal period.

The Liver of Control Rats:

Liver section obtained from a normal control animal, shows the hepatocytes arranged in cords or plates, one or two cells thick, radiating from the central vein. The central vein has extremely thin wall consisting of only one layer of endothelial cells. The spaces lying between these cords constitute the hepatic sinusoids. They are irregularly dilated vessels lined with flattened endothelial cells and few phagocytic cells namely vonkupffer cells. Liver lobules consist of the hepatocytes, which are the main building units of the liver. They are polyhedral in shape, enclosing a homogeneously fine granulated cytoplasm and large spherical nucleus with conspicuous nucleolus and distinct chromatin particles (Fig. A).

Rats received 43.2 mg carisprodol comp. /100g body weight showed a significant increase in liver enzymes ALT, AST, γ GT and ALP (P<0.001) as indicated in Table 8.

Table (7)
Effect of Chronic Administration of Carisoprodol Compound 21.6 mg /100g Body Weight on Serum ALT, AST, ALP and γ GT in Rats.

Groups \ Parameter		ALT (IU/L)	AST (IU/L)	ALP (IU/L)	γGT (IU/L)
Control	Range	(34.11-60.91)	(91.71-181.4)	(163.91-211.84)	(25.81-33.41
	Mean ±SD	45.39±7.6	134.71±6.32	193.74±7.2	28.94±2.6
D_{15}	Range	(30.91-55.14)	(105.41-197.21)	(170.93-222.1)	(20.14-44.51)
	Mean± SD	52.81±7.41	160.38±5.71	210.34±9.14	33.49±7.41
	% change	14.81	19.06	8.57	15.72
	P<	0.05	0.05	N.S.	0.05
D_{30}	Range	(33.74-69.15)	(190.35-204.71)	(179.3-314.0)	(24.91-47.19)
	Mean ± SD	60.41±5.94	188.59±7.14	260.45±7.13	40.15±6.43
	% change	32.41	39.99	34.43	38.74
	P<	0.01	0.01	0.01	0.01
D_{45}	Range	(41.81-73.82)	(180.45-310.64)	(190.31-320.7)	(27.91-60.43)
	Mean ± SD	70.91±6.84	204.798±9.73	301.45±10.34	55.14±8.13
	% change	56.22	51.95	55.59	90.53
	P<	0.001	0.001	0.001	0.001
W_{15}	Range	(49.93-73.45)	(181.9-210.41)	(181.79-307.4)	(30.13-57.41)
	Mean± SD	66.81±10.14	193.64±8.43	256.39±10.17	47.15±8.94
	% change	47.19	43.74	32.34	62.29
	P<	0.01	0.01	0.01	0.001

P- Value <0.05 statistically significant.
D_{15}, D_{30}, D_{45} = time duration by days.
W_{15}= withdrawal period.

Table (6)
Effect of Carisoprodol Compound 43.2 mg /100g Body Weight on Liver Oxidant/Antioxidant Status in Rats.

Groups \ Parameter		MDA nmol/g tissue	SOD u/g protein	CAT u/mg protein	GPX u/g protein	GR u/g protein
Control	Range	(36.89-41.35)	(626.07-652.33)	(142.92-150.36)	(179.25-187.4)	(70.55-74.28)
	Mean ±SD	40.01±2.34	640.17±3.45	149.13±2.17	180.15±2.11	71.84±2.75
D_{15}	Range	(41.93-54.91)	(435.11-613.14)	(121.25-133.6)	(162.36-166.85)	(60.29-67.99)
	Mean± SD	45.93±3.14	531.19±3.48	130.8±2.91	164.17±1.73	64.8±1.31
	% change	14.79	-17.02	-12.21	-8.87	-9.79
	P<	0.05	0.05	0.05	0.05	0.05
D_{30}	Range	(48.23-55.28)	(461.36-483.28)	(123.38-130.88)	(140.29-161.81)	(53.28-64.11)
	Mean ± SD	50.71±3.48	473.33±3.82	126.14±2.73	153.71±2.37	60.51±2.45
	% change	26.74	-216.06	-15.42	-14.68	-15.77
	P<	0.01	0.01	0.01	0.01	0.01
D_{45}	Range	(55.28-61.52)	(351.39-491.17)	(115.88-129.08)	(137.48-166.29)	(56.31-65.19)
	Mean± SD	60.14±3.11	447.13±3.14	120.34±2.61	141.71±2.9)	57.21±2.48
	% change	50.312	-30.15	-19.30	-21.34	-20.03
	P<	0.001	0.001	0.001	0.001	0.001
W_{15}	Range	(47.31-54.11)	(440.31-587.3)	(127. -140.9)	(145.1-167.3)	(50.14-66.93)
	Mean ±SD	49.1±13.17	456.13±3.13	132.71±2.91	150.91±2.74	62.13±2.47
	% change	22.74	-28.75	-11.01	-16.23	-13.52
	P<	0.01	0.01	0.05	0.01	0.05

P- Value <0.05 statistically significant.
D_{15}, D_{30}, D_{45} = time duration by days.
W_{15}= withdrawal period.

Table (7 and 8) showed that, serum aminotransferases (ALT and AST), alkaline phosphatase and γ-glutamyl transferase (γGT) activities were increased in their levels after carisoprodol comp. administration from D30 to D45 compared to sham group.

The changes in glutathione enzyme activity (GPX, GR) in the liver through the study period was shown in (Table 5and 6), the activity is lower in all groups than control group. During the administration, glutathione activity is near the normal values and reaches its lowest activity after 45 days. In the treated group, the patterns of change of glutathione activity show a significant decrease.

Table (5)
Effect of Carisoprodol Compound 21.6 mg / 100g Body Weight on Liver Oxidant / Antioxidant Status in Rats.

Groups \ Parameter		MDA nmol/g tissue	SOD u/g protein	CAT u/mg protein	GPX u/g protein	GR u/g protein
Cont	Range	(36.89-41.35)	(626.07-652.8)	(142.92-150.36)	(179.25-187.4)	(60.71-74.28)
	Mean ± SD	40.01±2.34	640.17±3.45	149.13±2.17	180.15±2.11	71.84±2.75
D_{15}	Range	(37.25-50.8)	(619.11-641.93)	(138.41-152.32)	(164.81-199.1)	(61.31-79.15)
	Mean ±SD	43.11±2.31	622.48±3.17	140.84±3.74	185.32±3.81	75.21±3.45
	% change	7.75	-2.763	-5.56	2.87	4.69
	P<	N.S.	N.S.	N.S.	N.S.	N.S.
D_{30}	Range	(41.98-53.11)	(501.9-630.93)	(128.81-147.91)	(159.32-183.1)	(59.13-70.19)
	Mean ± SD	46.793.41	540.734.12	133.32±2.81	169.312.15	62.21±3.93
	% change	16.95	-15.53	-10.60	-6.017	-14.79
	P<	0.05	0.05	N.S.	N.S.	0.05
D_{45}	Range	(38.91-54.93)	(401.9-530.93)	(111.91-146.91)	(148.31-161.81)	(54.31-66.11)
	Mean ± SD	50.19±3.14	508.4±3.75	129.78±2.15	161.23±2.91	59.19±2.74
	% change	25.444	-20.582	-12.97	-10.502	-17.61
	P<	0.01	0.01	0.05	0.05	0.01
W_{15}	Range	(30.48-43.59)	(601.34-640.15)	(119.81-161.31)	(173.41-191.25)	(58.84-81.31)
	Mean ± SD	38.79±2.94	613.19±3.84	153.28±3.17	183.45±3.19	74.39±3.81
	% change	-3.05	-4.21	2.78	1.83	3.549
	P<	N.S.	N.S.	N.S.	N.S.	N.S.

P- Value <0.05 statistically significant.
D_{15}, D_{30}, D_{45} = time duration by days.
W_{15}= withdrawal period.

Table (4)
Effect of Chronic Administration of Carisoprodol Compound 43.2mg /100g Body Weight on Serum Paraoxinase, CYTP450 Glutathione (Reduced and Oxidized) and GSH/GSSG Ratio in Rats.

Groups \ Parameter		Paraoxinase	CytP450	Glutathione (umol /L)			
		ng/100ml	ng/100	Reduced GSH	Oxidized GSSG	Total	GSH/ GSSG
Con.	Range Mean± SD	(40.51-56.11) 55.3±3.7	(51.81-66.42) 57.82±3.79	(3.14-4.89) 3.5±0.68	(2.74-3.91) 3.31±0.47	(6.31-7.84) 6.81±0.41	(0.91-1.31) 1.06±0.16
D_{15}	Range Mean± SD % change P<	(44.61-54.82) 50.4±2.1 -8.86 N.S.	(40.1-59.4) 45.7±3.91 -20.962 0.01	(2.41-4.59) 3.11±0.59 -11.14 0.01	(3.15-6.32) 3.47±0.81 4.833 N.S.	(5.31-6.91) 6.58±0.54 -3.38 N.S.	(0.54-0.81) 0.619±0.19 -43.0 0.001
D_{30}	Range Mean± SD % change P<	(34.15-50.21) 39.8±1.51 -29.48 0.001	(33.4-47.9) 39.11±2.94 -32.36 0.001	(1.8-3.45) 2.48±0.42 -29.14 0.001	(2.91-4.31) 3.58±0.61 8.16 0.05	(4.31-6.93) 6.06±0.81 -11.01 0.01	(0.63-0.94) 0.693±0.11 -34.62 0.001
D_{45}	Range Mean± SD % change P<	(33.18-40.29) 36.7±1.4 -33.63 0.001	(30.14-49.2) 38.14±3.11 -34.04 0.001	(1.67-2.91) 2.14±0.49 -38.86 0.001	(3.81-5.93) 3.975±0.73 16.73 0.001	(5.41-8.93) 6.12±0.97 -10.13 0.05	(0.31-0.54) 0.43±0.081 -59.43 0.0001
W_{15}	Range Mean± SD % change P<	(39.11-44.5) 43.15±2.34 -21.97 0.01	(31.9-57.1) 47.3±3.41 -17.122 0.01	(3.17-4.75) 3.6±0.61 2.86 N.S.	(3.41-8.39) 4.21±0.13 26.89 0.001	(9.32-11.41) 10.8±0.58 58.59 0.001	(0.43-0.58) 0.5±0.11 -52.83 0.001

P- Value <0.05 statistically significant.
D_{15}, D_{30}, D_{45} = time duration by days.
W_{15}= withdrawal period.

In the present study, chronic administration of carisoprodol comp. 21.6 and 43.2 mg body weight for 45 days resulted in a significant increase of lipid peroxidation (MDA) associated with a significant decrease in superoxide dismutase and catalase activities as shown in Table (5and6).

body weight, the withdrawal group (W**15**) was found to be significant (-17.122%, p<0.01).

In the present study, the two doses of carisoprodol comp. (21.6 and 43.2mg) produced a significant decrease in the activity of cytP450 depending on the dose and duration of time.

Depletion of serum glutathione levels especially by 43.2 mg/100g body weight (P<0.001) by- 38.86%, while the oxidized form (GSSG) recorded pronounced increase by 16.73% respectively.

The ratio GSH/GSSG represented significant decrease at all time of experiment when compared to control.

Table (3)

Effect of Chronic Administration of Carisoprodol Compound 21.6 mg /100g Body Weight on Serum Paraoxinase, CYTP450 Glutathione (Reduced and Oxidized) and GSH/GSSG Ratio in Rats.

Groups	Parameter	Paraoxinase	CytP450	Glutathione (umol /L)			
		ng/100ml	ng/100	Reduced GSH	Oxidized GSSG	Total	GSH/ GSSG
Control	Range Mean± SD	(40.51-56.11) 55.3±3.7	(51.81-66.42) 57.82±3.79	(3.14-4.89) 3.5±0.28	(2.74-3.91) 3.31±0.47	(6.31-7.84) 6.81±0.214	(0.91-1.31) 1.06±0.16
D_{15}	Range Mean± SD % change P<	(48.34-67.17) 57.4±3.41 3.797 N.S.	(49.32-63.21) 51.27±3.14 -11.32 0.05	(3.04-4.91) 3.61±0.14 3.047 N.S.	(2.41-4.19) 3.68±0.793 11.178 0.01	(6.98-8.34) 7.29±0.241 7.05 N.S.	(0.793-1.04) 0.981±0.17 -8.053 0.05
D_{30}	Range Mean± SD % change P<	(40.31-51.97) 45.61±3.11 -16.98 0.01	(41.11-50.93) 45.95±2.98 -19.46 0.01	(2.43-3.94) 3.19±0.11 -8.86 0.05	(3.19-4.78) 3.89±0.194 16.314 0.001	(6.88-7.21) 7.08±0.291 3.965 N.S.	(0.674-0.915) 0.829±0.19 -21.792 0.001
D_{45}	Range Mean± SD % change P<	(38.12-50.91) 44.05±3.24 -20.343 0.01	(30.94-54.81) 42.39±3.17 -26.69 0.001	(2.83-4.11) 3.05±0.287 -12.86 0.01	(3.43-5.35) 4.17±1.14 25.98 0.001	(6.74-7.34) 7.22±0.213 6.02 0.05	(0.694-0.937) 0.731±0.15 -31.04 0.001
W_{15}	Range Mean ± SD% change P<	(48.17-62.11) 53.29±2.94 -3.63 N.S.	(41.71-52.34) 50.71±3.71 -12.297 0.05	(3.11-4.93) 3.29±0.319 -6.0 N.S.	(2.75-4.19) 3.85±0.279 16.314 0.001	(7.04-7.23) 7.14±0.192 4.85 N.S.	(0.74-1.14) 0.855±0.17 -25.04 0.001

P- Value <0.05 statistically significant.

D_{15}, D_{30}, D_{45} = time duration by days.

W_{15}= withdrawal period.

Table(2)

Effect of Chronic Administration of Carisoprodol Compound 43.2 mg/100g Body Weight on Serum (IL-6) in Rats.

Groups \ Parameter		IL-6 (Pg/ml)
Control	Range	(42.13-69.91)
	Mean ± SD	63.49±3.41
D_{15}	Range	(100.19-145.43)
	Mean ± SD	122.63±4.53
	% change	93.149
	P<	0.001
D_{30}	Range	(115.32-167.41)
	Mean ± SD	153.11±5.2
	% change	141.16
	P<	0.001
D_{45}	Range	(160.11-284.39)
	Mean ± SD	202.2±4.59
	% change	218.47
	P<	0.001
W_{15}	Range	(88.34-114.91)
	Mean ± SD	101.74±5.13
	% change	154.75
	P<	0.001

P- Value <0.05 statistically significant.
D_{15}, D_{30}, D_{45} = time duration by days.
W_{15}= withdrawal period.

Tables (3 and 4) illustrated the effect of chronic administration of Carisoprodol comp.21.6 and 43.2 mg/100g body weight on serum paraoxinase, CYTP450 glutathione (reduced and oxidized) and GSH/GSSG ratio in rats.

A significant change in the activity of paraoxinase enzyme noted at D**30** and D**45** post administration of 21.6 mg carisoprodol comp. /100g body weight (-16.98%, P<0.01 and -20.343%, P<0.01). After 15 days withdrawal, the level was found to be replenished back to that of the sham group (Table 3),while in large dose 43.2 mg/100g

RESULTS

Effects of carisoprodol administration on serum interleukin- 6 (IL-6) were recorded in Tables (1 and 2). Results showed that the level of serum interlukin-6 (IL-6) was significantly increased ($p<0.001$) by both doses 21.6 mg and 43.2 mg/100g body weight after D15, D30 and D45 administration.

Table (1)
Effect of Chronic Administration of Carisoprodol Compound 21.6 mg/100g Body Weight on Serum (IL-6) in Rats.

Groups \ Parameter		IL-6 (Pg/ml)
Control	Range	(42.13-69.91)
	Mean ± SD	63.49±3.41
D_{15}	Range	(70.45-102.39)
	Mean ± SD	95.37±3.79
	% change	50.213
	P<	0.001
D_{30}	Range	(90.11-120.43)
	Mean ± SD	112.94±4.13
	% change	77.89
	P<	0.001
D_{45}	Range	(100.58-140.45)
	Mean ± SD	130.63±4.75
	% change	105.75
	P<	0.001
W_{15}	Range	(60.59-104.43)
	Mean ± SD	86.41±3.78
	% change	36.100
	P<	0.01

P- Value <0.05 statistically significant.
D_{15}, D_{30}, D_{45} = time duration by days. W_{15}= withdrawal period.

Serum levels of glutathione (oxidized and reduced) were estimated using a high performance liquid chromatography (HPLC) according to the method of Jayatilleke and Show (1993)[30].

Serum activities of alanine aminotranferase (ALT), asparatate aminotransferase (AST) were assayed by Bergmeyer and Bernt, (1974)[31] using commercial reagent kit from Biomerieux Co., France.

Alkaline phosphatase was assayed by (Tietz, 1982)[32].

γ- glutamyl transferase (GGT) activity was measured by kinetic colorimetric method using Boehringer Mannheim GmbH (Germany) kits according to the method of Szasz, (1969)[33].

Malondialdehyde (MDA) content in the liver was estimated by the method of Botsoglou, (1994)[34].

Catalase (CAT) activity was measured according to Sinha, (1972)[35].

Glutathione peroxidase activity (GPX) was measured by applying our standardized protocol using OXItek commercial kit [ZMC catalog # 0805002, ZeptoMetric Corporation, Buffalo NY,] based on Paglia and Valentine's method, (1967)[36] and **glutathione reductase (GR)** by Bompart *et al.*, (1990)[37].

Superoxide dismutase activity (SOD) was estimated by McCord and Fridovich, (1969)[38].

Serum cytP450 was estimated by Omura and Sato, (1964)[39].

Serum paraoxinase activity (antioxidant enzymes represent an important defense mechanism in diminishing the burden of the pro-oxidant stimuli by the drug) was estimated by Liang *et al.*, (2011)[40].

Histological Preparation:

Four micron cryostal section of rat liver was prepared and fixed on histological slides and stained with Mayer's eosin and haematoxylin[41].

Statistical analysis:

Results are expressed as mean ± SD. T-test was used to evaluate the significant difference between the normal control group and treated groups. Difference were considered significant when $P<0.05$.

followed by 15 days of withdrawal (w15)(27). These daily doses represented the human low therapeutic dose (i.e. one tablet taken three times daily) which provide 600 mg carisoprodol, 480 mg paracetamol and 96 mg caffeine, and the maximum daily dose (i.e. two tablets taken three times daily) which provide 1200 mg carisoprodol, 960 mg paracetamol and 192 mg caffeine). These therapeutic doses were calculated for rats according to Paget and Barnes (1964)(28) tables for species inter-conversion of dosage. All animals were scarified after 30 minutes from the last administration, the blood and liver tissue samples were immediately collected. Sera were then separated by centrifugation and kept at -20 till analysis. Livers were excised; the same lobe was chosen and divided into two parts. One part kept in formalin for histological examination and the other part homogenized for biochemical analysis determination and kept at -200C till analysis.

Sample Preparation for Biochemical Analysis:

Liver was rapidly isolated, weighed and homogenized in 4 volumes ice cold bidistilled water (20% w/v homogenate) using a Teflon homogenizer. A portion of the homogenate was mixed with a cold 2.3% KCl solution, centrifuged at 1000xg at 4C for 15 minutes; the supernatant was used for MDA analysis. Another portion of the homogenate was mixed with 7.5% sulphosalicylic acid, centrifuged at 6000xg for 15 minutes and the resulting protein-free supernatant was used for the estimation of glutathione (GSH) level. The last portion of the homogenate was mixed with Tris EDTA buffer, pH 7.6, centrifuged at 15000xg at 4C for 30 minutes using Dupont sor vall ultracentrifuge (USA). The resulting supernatant (the cytosolic fraction) is used for the determination of glutathione reductase, (GR), glutathione peroxidase (GPX), catalase and superoxide dismutase (SOD).

Biochemical Analysis:

Serum interleukin-6 (IL-6) was determined by enzyme immunoassay (ELISA)[29], as it is considered as an "alarm hormone" that reflects an endothelial cell injury probably mediated by the toxins of the drug.

As the drug has been noticed to be abused among teen agers as an inexpensive alternative to illicit drugs, some countries like Norway was taken off carisoprodol compound (200 mg carisoprodol, 160 mg paracetamol, 32 mg caffeine) from the Norwegian market because the therapeutic advantages of the drug were perceived as fewer than the drawbacks, the drug was often abused[26]. In Egypt, the drug use attracted some interest in drug addiction field and sold over- the-counter despite of its regulation (Guide book for controlled and uncontrolled drugs, 2003) and some drug policies does not favor combination preparations. **So, the present study aims to evaluate the toxic effect induced by carisoprodol compound drug on oxidative/ anti-oxidative processes of the liver of male rats, and some immune responses were also investigated.**

Materials and methods

Chemicals and Kits: All chemical used in the present study were purchased from BDH Chemical Ltd., Pools (England). All utilized kits were obtained from BioMerieux laboratory reagents and products (France) and Boehringer, Mannheim GmbH (Germany).

Carisoprodol compound: Crisoprodol compound drug (somadril compound) was obtained as tablets of a combination product containing carisoprodol 200 mg, paracetamol 160 mg and caffeine 32 mg from Mina Pharm for pharmaceuticals and Chemical industries, Cairo, A.R.E.

Animals

100 male Sprague Dawley rats weighed about (100-150 g body weight.) were obtained from experimental animal house, Helwan, Egypt. Animals were maintained on a normal rat chows ad libitum during the experimental period. They were allowed free access to water. The animals were divided into three groups, one group served as control (20 rats) and administered oral doses of corn oil for 45 days. The other two groups served as treated (40 rats in each group) and administered oral daily doses of carisoprodol compound suspended in corn oil equal to 21.6 mg and 43.2 mg/100 mg body weight of rat respectively for 15, 30 and 45 days. The 45-days treatment was

products— hydroxycarisoprodol, hydroxymeprobamate, and meprobamate were the major metabolites identified in the blood and urine[16].

Carisoprodol have a narrow therapeutic range[17] and when carisoprodol ingested with other medications, may be a contributing factor in death, even when present at therapeutic concentrations[18].

Paracetamol (acetaminophen) is a widely used over-the-counter drug for analgesic and antipyretic effects. Its use in overdose (suicidal or accidental) or with chronic alcohol abuse causes fulminant liver failure[19]. Paracetamol induced hepatic failure is the second leading cause of liver transplantation[20]. It is metabolically activated by cytochrome P450 enzymes to a reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI)[21]. Also, paracetamol is a frequent component in many over-the-counter and prescription combinations with decongestants and/or antihistamines for cold and allergy symptoms, or as a sleeping aid and with other analgesics (such as oxycodone and codeine) for moderate-to-severe forms of pain[22].

Caffeine is a central nervous system and metabolic stimulant and is used both recreationally and medically to reduce physical fatigue and to restore alertness when drowsiness occurs[23]. It is metabolized in the liver by the cytochrome P450 oxidase enzyme system (to be specific, the 1A2 isozyme) into three metabolic dimethylxanthines, ,each of which has its own effects on the body: Paraxanthine (84%): Increases lipolysis, leading to elevated glycerol and free fatty acid levels in the blood plasma. Theobromine (12%): Dilates blood vessels and increases urine volume. Theobromine is also the principal alkaloid in the cocoa bean, and therefore chocolate. Theophylline (4%): Relaxes smooth muscles of the bronchi, and is used to treat asthma. The therapeutic dose of theophylline, however, is many times greater than the levels attained from caffeine metabolism. Each of these metabolites is further metabolized and then excreted in the urine. Caffeine can accumulate in individuals with severe liver disease, increasing its half-life[24]. Caffeine overdose can result in a state of central nervous system over-stimulation called caffeine intoxication[25].

Carisoprodol, the main active ingredient, was introduced in the pre benzodiazepine era as an alternative to the problematic barbiturates and barbiturate-like drugs as carisoprodol was chemically based on the barbiturate-like drug meprobamate and the main metabolite in man was actually meprobamate[8]. Despite the prevalence of carisoprodol abuse, its mechanism of action remains unclear. Its sedative effects which contribute to its therapeutic and recreational use are generally to the actions of its primary metabolite meprobamate at GABA (A) receptors (GABA"A"R)[9]. Although carisoprodol itself is not controlled on the federal level, its active metabolite, meprobamate is an addictive sedative and a schedule IV controlled substance[10]. Meprobamate (Miltown®, Equanil®) is a sedative-hypnotic that was commonly used in the treatment of anxiety before its classification as a schedule IV controlled substance at the federal level. It thus has been generally accepted that both the therapeutic effects of carisoprodol and those that underlie its abuse potential are due to its conversion to meprobamate by the cytochrome P_{450} enzyme $CytP_2C_{19}$[11].

Carisoprodol produces tolerance and a significant withdrawal syndrome[12]. Its abuse is associated with psychomotor impairment leading to arrests for "driving under the influence" as well as increased risk of automobile accidents[13]. In spite of significant restriction for the use of carisoprodol as a monosubstance, the concomitant withdrawal of several centrally acting analgesic products in fact led to the increased use of carisoprodol[14]. In the absence of GABA, carisoprodol produced picrotoxin-sensitive, inward currents that were significantly larger than those produced by meprobamate, suggesting carisoprodol may directly produce GABAergic effects in vivo[15].

Carisoprodol is rapidly absorbed from the gastrointestinal tract. A single gavage dose of carisoprodol produced a peak blood concentration in approximately 30 to 60 minutes in rats. Approximately 55% of carisoprodol was bound to plasma protein. The injected carisoprodol was distributed throughout the body within 10 minutes. It undergoes hepatic biotransformation by the cytochrome P450 enzyme 2C19 (CYP2C19) encoded by polymorphic Cyt P_2C_{19} gene, hydroxylation and N-dealkylation produce three metabolic

Introduction:

Liver injury caused by toxic chemicals and certain drugs has been recognized as a toxicological problem. Hepatotoxicity is one of a very common aliment resulting into serious debilities ranging from severe metabolic disorders to even mortality[1]. Carisoprodol compound (somadril compound) is a muscle relaxant antispasmodic that indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions in adults[2]. This drug has recently been noticed to be abused among teen agers as an inexpensive alternative to illicit drugs[3].

Carisoprodol compound is marketed under a variety of brand names such as Somadril, Soma, Somacid, Somanil, Somalgit, Vanadam, Sanoma, Sodol. It was available both as a mono-substance in a tablet containing 350 mg (Somadril)^{R} and as carisoprodol compound contains different active ingredients as follows: (Somadril comp)^{R} tablets contain carisoprodol 200 mg, Paracetamol (acetaminophen) 160 mg and Caffeine 32 mg [4] and (Soma comp) ^{R} tablets which contain carisoprodol 200 mg and Asprin 325 mg with or without 16mg codeine phosphate (Meda Pharmaceutical Inc.). The recommended dose of carisoprodol compound is 1 or 2 tablets, 3 times daily in adults and the recommended maximum duration of use is up to two or three weeks[5].

Carisoprodol is sold in most countries. Some countries like Spain sell it over- the – counter (no prescription needed) but in most countries a prescription is required[6]. In Egypt, Carisoprodol is available as Somadril compound contains carisoprodol 200 mg, paracetamol 160 mg and caffeine 32 mg. It is a prescribed drug produced by Mina Pharm for pharmaceutical and chemical industries. It is classified schedule 2 pharmaceutical regulations by the decision of the Minister of health and population No. 172 of the year 2011, while, meprobamate the active metabolite of carisoprodol[7] is a schedule III controlled substance on Anti-drug law No.182 of the year 1960.

BIOCHEMICAL AND HISTOLOGICAL CHANGES IN MALE ALBINO RATS RECEIVING ORAL CARISOPRODOL COMPOUND DRUG

Laila Abed El Kawy*

Background: Carisoprodol compound (Somadril compound)^{R} is a widely used skeletal muscle relaxant and analgesic and is available as a prescription drug. **Aim of the work:** The present study aims to evaluate the toxic effect induced by carisoprodol compound drug on oxidative/ anti-oxidative processes of the liver of male rats, and some immune responses were also investigated. **Materials and methods**: Adult male Sprague Dawley rats were orally administrated (21.6 mg and 43.2 mg /100 g rat body weight) of carisoprodol compound tablets in corn oil corresponding to therapeutic and supratherapeutic doses in human by gastric gavage for 15, 30 and 45 days. The 45-days treatment was followed by 15 days withdrawal (w15). Levels of markers indicative of hepatotoxicity such as enzymes of liver functions activity, levels of serum glutathione (reduced and oxidized) as index of redox system were assayed. In addition, the activity of serum paraoxinase enzyme , cytP_{450} , IL-6 and oxidant/ antioxidant status which was assessed in liver by measuring the levels of malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), and catalase (CAT) were assayed. Moreover, histological liver changes were examined. **Results**: The results showed a significant elevation in serum ALT, AST, γGT and ALP in carisoprodol compound treated rats versus control groups. In comparison with the control findings of male rats, carisoprodol treated male rats showed significant increase in MDA content by 50.312% and a significant reduction in GR by -20.03% with observed significant inhibition in catalase activity by -19.30%. Also, significant inhibition in SOD activity was achieved in carisoprodol -treated male rats by - 30.15% versus control groups. GSH concentration was significantly decreased at D_{15}, D_{30} and D_{45} and W_{15}, while the level of oxidized form was significantly increased and also GSH/GSSG ratio was decreased at D_{15}, D_{30}, D_{45} and W_{15} post administration when compared to control group. Serum activity of paraoxinase and cytp_{450} was significantly decreased. Histological examination of liver tissue in carisoprodol treated male rats significantly revealed marked changes included focal and confluent necrosis, portal tract inflammation and steotosis. **Conclusion**: These deleterious changes give an alarm to be aware in using such drug for a long time as its consumption may be contributed to health hazards and must be used with strict health precaution.

---

* Lecturer, Narcotic Research Department, The National Center for Social and Criminological Research.