Trop J Nat Prod Res, February 2025; 9(2):541 - 544 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Short Communication

Evaluation of Oxidative Stress Levels in Codeine-Induced and Codeine Recovery Phase of Albino Rats

Chiagozie C King-Bertram[1], Esther I Etu[2], Nyejirime Y Wike.[3], Achi U Franklyn[4], Ukamaka P Obichukwu-Ehighibe[1], Ndubuisi N Richards[5], Chinedu P Maduka [1], Chukwu D Chigozie[6], Ekoh, J Adaorah[7], Chinonso C Ani[8], Afun I Olabanji[9], Emmanuel A Ameh[10], Maria C Ugwuodo[11], Omolola M Stephen [12], Ngozi R Esenwa[13]

[1]*Department of Medical Laboratory Science, Faculty of Health Science and Technology, University of Nigeria, Enugu Campus, Enugu State*
[2]*Department of Anatomic Pathology, Faculty of Basic Clinical Science, Alex Ekwueme Federal University, Ndufu Alike, Ebonyi State*
[3]*Department of Human Physiology, Faculty of Basic Medical Science, State University of Medical and Applied Science, Igbo-eno, Enugu State*
[4]*Department of Morbid Anatomy, Faculty of Medical Laboratory Science, University of Nigeria Teaching Hospital Enugu State*
[5]*Department of Science Laboratory Technology, University of Nigeria, Nsukka, Enugu State*
[6]*Department of Medical Laboratory Science, Faculty of Health Science, David Umahi Federal University of Medical Science, Uburu Ebonyi State*
[7]*Department of Histopathology, Enugu State University Teaching Hospital, Parklane, Enugu State*
[8]*Department of Nursing (Adult), Faculty of Health and Social Work, University of Hertfordshire, England*
[9]*Department of Science Education, Faculty of Environmental and Education, University of Abuja*
[10]*Department of Medical Services, Akanu Ibiam Federal Polytechnic Unwana, Ebonyi State*
[11]*Department of Histopathology Faculty of Basic Clinical Sciences, Enugu State University College of Medicine, Enugu State*
[12]*Department of Microbiology, Faculty of Science, Engineering and Technology, Osun State University, Osun State*
[13]*Department of Marine Sciences, Faculty of Science, University of Lagos, Lagos State*

ARTICLE INFO

Article history:
Received 23 September 2024
Revised 10 October 2024
Accepted 28 December 2024
Published online 01 March 2025

ABSTRACT

The widespread availability and potential for misuse of codeine have rendered chronic use a pressing public health issue. Long-term codeine exposure can lead to multisystem toxicity, causing oxidative stress, cellular damage, and increased vulnerability to illness. This study assessed the levels of oxidative stress in Albino rats during the codeine-induced and codeine-recovery phases. For this study, 20 Albino rats weighing 160-200 g were used. The animals were assigned into four groups of five rats. Feed and water were administered to rats in Group 1 (control). Codeine was administered to Groups 2, 3, and 4 at doses of 10 mg/kg, 15 mg/kg, and 20 mg/kg body weight, respectively. Serum biochemical assays were conducted using blood samples collected on day 14. After that, the animals underwent a 7-day codeine withdrawal to assess recovery. Blood samples were collected on day 7 for the second phase of biochemical assay. Administration of codeine for 14 days significantly reduced antioxidant enzyme levels (superoxide dismutase, glutathione reductase, catalase, and glutathione peroxidase) ($p < 0.05$), but serum lipid peroxidation level was elevated ($p < 0.05$). After a 7-day recovery period, catalase, glutathione reductase, and glutathione peroxidase levels showed significant recovery ($p < 0.05$), lipid peroxidation decreased significantly ($p < 0.05$), but superoxide dismutase levels remained unchanged. These findings indicate that misuse of codeine adversely affects oxidative stress levels, persisting even after recovery. Therefore, caution is recommended when consuming codeine and other opioids.

Keywords: Codeine, Oxidative stress, Catalase, Superoxide dismutase, Lipid peroxidation.

Introduction

The profound effects of opioid use on cellular and physiological processes have sparked widespread concern, particularly in instances of prolonged or excessive consumption.[1] Codeine, a potent opioid, significantly contributes to the global opioid crisis due to its high potential for misuse.

*Corresponding author. Email: nyejirime.wike@sumas.edu.ng
Tel: +2348167044210

Citation: King-Bertram CC, Etu EI, Wike NY, Franklyn AU, Obichukwu-Ehighibe UP, Ndubuisi RN, Maduka CP, Chigozie CD, Adaorah EJ, Ani CC, Olabanji AI, Ameh EA, Ugwuodo MC, Stephen OM, Esenwa NR. Evaluation of Oxidative Stress Levels in Codeine-Induced and Codeine Recovery Phase of Albino Rats. Trop J Nat Prod Res. 2025; 9(2): 541 – 544 https://doi.org/10.26538/tjnpr/v9i2.18

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

Pharmacy practitioners have raised concerns regarding patient requests for over-the-counter codeine, citing an inadequate awareness of its deleterious health consequences and dependency risks.[2] The misuse of codeine-containing products is prevalent across various demographics, including pharmacy professionals, medical students, and the public. This misuse often stems from a lack of awareness regarding the risks of dependence and the ease of access to these medications, particularly in over-the-counter formats.[2] The widespread availability and potential for misuse of codeine have rendered chronic use a pressing public health issue.[3-4] Long-term codeine exposure can precipitate multisystem toxicity, fostering oxidative stress and consequent cellular damage, thereby increasing vulnerability to various diseases. Opioid-induced physical dependence, exemplified by codeine, is characterised by adaptive changes culminating in withdrawal symptoms upon cessation.[3] Moreover, opioid withdrawal and physical dependence induce cellular and neural circuit modifications, underpinning addiction-related behaviours.[5] Protein deterioration, mutations in DNA, and the breakdown of lipids are all ways that oxidative stress damages cells. It results from a mismatch between the generation of reactive oxygen species and antioxidant defences.[6-7] In addition to contributing to the

emergence of cancer, heart attack, neurodegeneration, and other disorders, this stress is linked to tissue damage in several organs, including the liver, kidneys, brain, and lungs.[8-10,7] Certain pharmaceuticals, notably those with high metabolic demands or toxic metabolites, can exacerbate oxidative stress, heightening susceptibility to organ dysfunction and disease.[11] Heavy metal exposure also induces oxidative damage.[12] Despite codeine's classification as a mild opioid, chronic use has been linked to oxidative stress and tissue damage.[13-14] However, the dynamics of oxidative stress during prolonged codeine exposure and recovery remain poorly understood. Elucidating the relationship between codeine exposure, oxidative stress, and recovery is essential for developing effective treatment and recovery strategies to manage codeine dependency. This study investigated the oxidative stress levels in albino rats administered with codeine. Key oxidative stress markers, including lipid peroxidase (LPO), catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), as well as glutathione reductase (GR), were evaluated to elucidate codeine-induced changes upon cessation of exposure.

Materials and Method

Drug description
Dihydrocodeine Tablets 30 mg (Dihydrocodeine BP) (DF 118) were obtained from Alpha Pharmacy, No 44 Ogui Road, Enugu, Enugu State. Dihydrocodeine tablets are white, flat, circular tablets with a bevel edge and a break-line on one side, each containing Dihydrocodeine BP 30 mg.

Animal
This study used 20 male Wistar rats weighing 160–200 g at the Brain-Phosphorylation Research and Training Centre in Enugu State, Nigeria. The rats were acclimated for 10 days, provided unlimited access to water and standard Top Feed, and housed under controlled laboratory conditions. The experiment adhered to international laboratory animal care and use standards, with ethical clearance obtained from the University of Nigeria's Animal Welfare and Ethics Committee.

Experimental Design
The rats were assigned into four groups of 5 according to their body weight. The administration was done through an oral route using an oral cannula made from 1 mL plastic syringes, and the experiment lasted for 21 days. The animals in group 1 (Control group) received 0.5 mL of normal saline. Those in groups 2, 3, and 4 received 10mg/kg, 15mg/kg, and 20mg/kg body weight of codeine, respectively.

Oxidative Stress Assay
Superoxide dismutase (SOD) activity was assayed by employing the procedure of Sun *et al.*[15] with a Randox Kit. The assay added 15 µL of serum, standard, and distilled water to labelled test tubes. A mixed substrate (500 µL) was added, followed by xanthine oxidase (75 µL). The initial absorbance was measured at 30 seconds, and the final absorbance was recorded after 3 minutes at 505 nm. The standard curve was used to calculate the SOD activity in units per gram of haemoglobin.

Assay of catalase
Aebi's technique[16] was used to measure catalase activity. 0.9 mL of distilled water, 0.1 mL of plasma, 2 mL of H_2O_2, and 2 mL of phosphate buffer (pH 7) were combined in a test tube for the assay. A 1 mL portion of the mixture was mixed with the dichromate acetic acid reagent to start the reaction. For two minutes, absorbance was measured at 30-second intervals. The unit of measurement for catalase activity was U/mL of plasma, where U is the number of micromoles of H_2O_2 used in a second.

Determination of the glutathione concentration
Paglia's approach[17] was used to measure glutathione levels. 0.9 mL of distilled water, 0.02 mL of sodium sulphate, and 0.1 mL of blood sample were combined. Following two minutes of standing at the ambient temperature and shaking, 0.02 mL of 20% lithium sulphate, 0.2 mL of 20% $NaCO_3$, and 0.2 mL of phosphor-18-tungstic acid were introduced. The mixture was shaken and left for four minutes for maximum colour development. After adding 2.5 mL of 20% sodium sulphate, the absorbance at 680 nm was determined ten minutes later. Additionally, a blank sample was made using water rather than blood, and the glutathione level was determined using the conventional cysteine curve.

Estimation of the extent of lipid peroxidation (malondialdehyde)
The method previously described by Beuge and Aust[18] was employed in this assay. The level of malondialdehyde (MDA) was measured to quantify lipid peroxidation. 10 µL of serum and 10 µL of distilled water were introduced to each of the three test tubes marked "test" and "blank." Next, 0.5 mL of 1% TBA (thiobarbituric acid) and 0.5 mL of 25% TCA (trichloroacetic acid) were incorporated into 0.3% NaOH. After 40 minutes of boiling in a water bath, the mixture was chilled in cold water. After the solution had cooled, 0.1 mL of 20% sodium dodecyl sulfate was included and thoroughly mixed. The absorbance of the mixture was measured at the wavelengths of 532 nm and 600 nm in relation to a blank.

Statistical analysis
Data analysis was performed using SPSS version 20. Results were expressed as mean ± standard error of the mean (SEM). Statistical significance was set at $p < 0.05$.

Results and Discussion

This study investigated oxidative stress levels in albino rats during the codeine-induced and recovery phases. In Table 1, which represents the codeine-induced phase, the mean values of SOD in Groups 2 and 4 were 10.17 ± 0.30 and 8.78 ± 0.24, respectively, when compared to the control (10.74 ± 0.36) and Group 3 (9.64 ± 0.22), indicating a statistically significant difference ($p< 0.05$). For CAT, the mean values for Groups 2, 3, and 4 were 2.21 ± 0.08, 1.97 ± 0.10, and 2.26 ± 0.30, respectively, while the mean value for the control group was 4.74 ± 0.34. This indicates a statistically significant difference ($p< 0.05$) across all the groups compared to the control. The mean values observed for GR were statistically significant ($p< 0.05$) across the groups compared to the control. The mean values for Groups 2, 3, and 4 were 7.21 ± 0.28, 4.04 ± 0.24, and 4.90 ± 0.57, respectively, while a mean value of 9.41 ± 0.26 was observed in the control. For GPx, the mean values for Groups 2, 3, and 4 were 11.12 ± 0.43, 9.74 ± 0.15, 9.91 ± 0.23, respectively, while that of the control was 19.23 ± 0.42, indicating a statistically significant difference ($p< 0.05$). Additionally, there was a statistically significant difference ($p< 0.05$) in the mean values of LPO across the groups, 4.56 ± 0.40, 6.77 ± 0.14, and 8.37 ± 0.29, respectively, while the control had a mean value of 1.81 ± 0.16. In Table 2, which represents the mean levels of oxidative stress markers after the recovery period, there was no statistically significant difference ($p< 0.05$) observed in SOD levels of both the control and experimental groups. For CAT, the values observed in the 3 groups, 2.73 ± 0.30, 3.27 ± 0.42, and 3.40 ± 0.81, revealed a statistically significant difference ($p< 0.05$) when compared with the control 4.75 ± 0.70. The mean levels of GR also indicated a statistically significant difference ($p< 0.05$) with values of 6.79 ± 0.18, 4.76 ± 0.76, 8.69 ± 0.27, in Groups 2, 3 and 4, respectively. In GPx and LPO levels, a statistically significant difference ($p< 0.05$) was observed in the experimental groups when compared with the control. The corresponding mean values are 13.49 ± 0.40, 11.12 ± 0.73, and 10.68 ± 0.19 for experimental groups in GPx and 3.45 ± 0.38, 5.20 ± 0.35, 6.10 ± 0.31 for LPO. The mean values for control were 19.41 ± 0.40 and 2.64 ± 0.14, respectively. Numerous metabolic and neurological degenerative diseases have been linked to oxidative stress.[7] Compared to the group with no treatment, codeine administration degraded the antioxidants, increasing the production of reactive substances such as hydrogen peroxide, which are linked to the onset of oxidative stress. While LPO concentrations rose, those of SOD, CAT, GR, and GPx sharply declined. This is in agreement with the studies done by.[19-21] The same effect was observed on the oxidative stress markers after the 7-day withdrawal period. Codeine administration for 14 days and the codeine recovery phase after 7 days significantly reduced SOD concentrations, inducing oxidative stress. This aligns with the study done by Younus.[22]

Table 1: Oxidative stress markers after 14-day treatment with codeine

	OXIDATIVE STRESS MARKERS				
GROUP	SOD(U/L)	CAT(U/L)	GR (mg/dl)	GPx(U/L)	LPO (mg/dl)
1 (control)	10.74 ± 0.36	4.74 ± 0.34	9.41 ± 0.26	19.23 ± 0.42	1.81 ± 0.16
2 COD (10 mg)	10.17 ± 0.30^{*4}	2.21 ± 0.08^{**1}	7.21 ± 0.28^{*1,3,4}	11.12 ± 0.43^{*1,3}	4.56 ± 0.40^{**1,3,4}
3 COD (15 mg)	9.64 ± 0.22	1.97 ± 0.10^{**1}	4.04 ± 0.24^{**1,2}	9.74 ± 0.15^{*1,2}	6.77 ± 0.14^{**1,2,4}
4 COD (20 mg)	8.78 ± 0.24^{*1,2}	2.26 ± 0.30^{**1}	4.90 ± 0.57^{*1,2}	9.91 ± 0.23^{**1}	8.37 ± 0.29^{**1,2,3}

Values are given as mean ± standard error of the mean (SEM). COD = Codeine. The significance level for the P value was set at $p < 0.05$. *= $p < 0.05$; **= $p < 0.001$

Table 2: Oxidative stress markers after 7 days recovery period from treatment with codeine

	OXIDATIVE STRESS MARKERS				
GROUP	SOD(U/L)	CAT(U/L)	GR (mg/dl)	GPx(U/L)	LPO (mg/dl)
1 (control)	11.13 ± 0.36	4.75 ± 0.70	9.63 ± 0.18	19.41 ± 0.40	2.64 ± 0.14
2 COD (10 mg)	10.96 ± 0.24	2.73 ± 0.30*^{1}	6.79 ± 0.18^{*1,3,4}	13.49 ± 0.40^{*1,3,4}	3.45 ± 0.38^{*3,4}
3 COD (15 mg)	10.96 ± 0.20	3.27 ± 0.42^{*1,2,4}	4.76 ± 0.76^{*1,2}	11.12 ± 0.73^{*1,2}	5.20 ± 0.35^{*1,2}
4 COD (20 mg)	11.07 ± 0.07	3.40 ± 0.81^{*2,3}	8.69 ± 0.27^{*1,2}	10.68 ± 0.19^{*1,2}	6.10 ± 0.31^{*1,2}

Values are given as mean ± standard error of the mean (SEM). COD = Codeine. The significance level for the P value was set at $p < 0.05$. *= $p < 0.05$; **= $p < 0.001$

High SOD concentrations within the cells are essential for antioxidant defence against oxidative stress.[23] Reduced superoxide dismutase (SOD) activity has been linked to various health conditions, particularly those involving oxidative stress and inflammation. This enzyme mitigates oxidative damage by converting superoxide radicals into less harmful molecules. Poorer SOD activity was linked to a poorer left ventricular ejection fraction (LVEF) in individuals with acute coronary syndrome and type 2 diabetes, suggesting that this could be a predictive indicator of cardiovascular risk.[24] Treatment with codeine decreased CAT concentrations. CAT plays a critical role in shielding oxygen-dependent cells from oxidative damage by breaking down hydrogen peroxide. Degenerative disorders are associated with catalase dysfunction or deficiency.[25] Cells' reaction to oxidative stress is significantly influenced by glutathione reductase (GR).[26] Codeine decreased GR activity, which impacted the size of the GSH pool and caused oxidative stress that damaged cells and organs. This validates the study conducted by Lin *et al*.[27] The inhibition of glutathione reductase (GR) significantly impacts cellular responses during viral infections by altering redox homeostasis and influencing cell death pathways.[27-28] A Similar result was observed after 7 days of withdrawal from codeine. GPx activity significantly decreased following codeine exposure as well as the recovery phase. In addition to oxidising glutathione to glutathione disulfide, GPx is crucial in reducing peroxide produced by hydrogen and lipid peroxidase to water and lipid alcohol, respectively.[29–30] Damage to organs results from an increase in peroxide from hydrogen and lipid peroxidase caused by insufficient action of GPx or glutathione concentrations.[29] In line with the tramadol research carried out by Ogili *et al*.[20], codeine raised LPO concentrations. Elevated lipid peroxidation (LPO) is a significant biochemical process linked to various health conditions, including neurodegenerative diseases, cancer, and inflammatory disorders. This oxidative lipid breakdown has been linked to the aetiology of several disorders and can cause harm to cells. Elevated ferritin levels were related to higher LPO in adult-onset Still's disease, suggesting a connection between inflammation and oxidative stress.[31] Increased unsaturated lipids have been linked to heightened lipid aldehyde levels in brain regions affected by synucleinopathies, including those with Parkinson's.[32]

Conclusion

The codeine-induced and recovery phases resulted in significantly decreased oxidative stress levels. Long-term abuse of codeine can harm oxidative stress markers irreparably, harming organs and impairing immunological function. However, as this study focused on short-term recovery, additional study is required to examine the consequences of protracted recovery from codeine use. This study's limitation is the scarcity of supporting literature on oxidative stress levels during a codeine recovery phase. Further research should be carried out on long-term codeine treatment and recovery phase on vital organs and oxidative stress levels.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

References

1. Paltov Ye, Masna Z, Horbova N. Normal Indicators of Oxidative Stress and The Dynamics of Their Changes at Different Terms of Experimental Opioid Influence. Clin Anat and Oper Surg. 2022; 21(3), 22-28. doi: 10.24061/1727-0847.
2. Bronkhorst E, Adamjee M, Poka M. The misuse of codeine-containing medicines: Perceptions and behaviours of qualified pharmacy professionals. S Afr Fam Pract. 2024;10;66(1): e1-e7. doi: 10.4102/safp. v66i1.5862.
3. Kirschbaum M, Barnett T, Cross M. Experiences of over-the-counter codeine misusers and accounts of recovery: A qualitative study in Tasmania, Australia. Drug Alc Rev. 2020;39(7):879-887. doi: 10.1111/dar.13081.

4. Archibong VB, Usman IM, Lemuel AM. Prolonged Codeine Administration Causes Degeneration of Myelinated Axons and Motor Dysfunction in Wistar Rats. Subst Abuse Rehabil. 2022; 13:73-81. doi: 10.2147/SAR.S365982.
5. Thompson BL, Oscar-Berman M, Kaplan GB. Opioid-induced structural and functional plasticity of medium-spiny neurons in the nucleus accumbens. Neurosci Biobehav Rev. 2021; 120:417-430. doi: 10.1016/j.neubiorev.2020.10.015
6. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F, Altavilla D, Bitto A. Oxidative Stress: Harms and Benefits for Human Health. Oxid Med Cell Longev. 2017; 2017:8416763. doi: 10.1155/2017/8416763.
7. Jomova K, Raptova R, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, Valko M. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and ageing. Arch Toxicol. 2023; 97(10), 2499–2574. https://doi.org/10.1007/s00204-023-03562-9
8. Muscolo A, Mariateresa O, Giulio T, Mariateresa R. Oxidative Stress: The Role of Antioxidant Phytochemicals in the Prevention and Treatment of Diseases. Int. J. Mol. Sci. 2024; *25*, 3264. https://doi.org/10.3390/ijms25063264
9. Singh A, Kukreti R, Saso L, Kukreti S. Oxidative Stress: A Key Modulator in Neurodegenerative Diseases. Mol. 2019;24(8):1583.
10. Murphy MP, Bayir H, Belousov V, Chang CJ, Davies KJA, Davies MJ, Dick TP, Finkel T, Forman HJ, Janssen-Heininger Y, Gems D, Kagan VE, Kalyanaraman B, Larsson NG, Milne GL, Nyström T, Poulsen HE, Radi R, Van Remmen H, Schumacker PT, Thornalley PJ, Toyokuni S, Winterbourn CC, Yin H, Halliwell B. Guidelines for measuring reactive oxygen species and oxidative damage in cells and *in vivo.* Nat Metab. 2022;4(6):651-662. doi:10.1038/s42255-022-00591-z
11. Dokunmu TM, Opara SC, Awani OU, Enoma DO, Adelani BI, Rotimi OA, Yakubu OF. Effects of Caffeine-Artemisinin Combination on Liver Function and Oxidative Stress in Selected Organs in 7,12- Dimethylbenzanthracene-Treated Rats. Trop J Nat Prod Res. 2021; 5(5):963-969. doi.org/10.26538/tjnpr/v5i5.27
12. Sriramcharan P, Jawahar N, Rajeshkumar R, Arivuselvam R, Antony J, Ganganagappa N, Venkatachalam S. Effects of Cerium Oxide and Selected Heavy Metals on the Induction of Cell Death Via Oxidative Stress-Mediated DNA Damage. Trop J Nat Prod Res. 2022; 6(7): 1108-1112.doi.org/10.26538/tjnpr/v6i7.11
13. Zahmatkesh M, Kadkhodaee M, Salarian A, Seifi B, Adeli S. Impact of opioids on oxidative status and related signalling pathways: An integrated view. J Opioid Manag. 2017;13(4):241-251. doi:10.5055/jom.2017.0392.
14. Mohammadnejad L, Soltaninejad K. Tramadol-induced organ toxicity via oxidative stress: a review study. International Journal of Medical Toxicology and Forensic Med. 2022;12(1):35430.
15. Sun Y, Oberley LW, Li Y. A simple method for clinical assay of superoxide dismutase. Clin Chem. 1988;34(3):497-500.
16. Aebi H. Catalase in vitro. Methods Enzymol. 1984; 105:121-126. doi:10.1016/s0076-6879(84)05016-3
17. Paglia DE, Valentine WN. Studies on the quantitative and qualitative characterisation of erythrocyte glutathione peroxidase. J Lab Clin Med. 1967;70(1):158-169.
18. Buege JA, Aust SD. Microsomal lipid peroxidation. Methods Enzymol. 1978; 52:302-310. doi:10.1016/s0076-6879(78)52032-6
19. Ajayi AF, Akhigbe RE. Codeine-induced sperm DNA damage is mediated predominantly by oxidative stress rather than apoptosis. Redox Rep. 2020;25(1):33-40. doi: 10.1080/13510002.2020.1752003.
20. Ogili F, Ali D, Attamah G, Aletan U, Nwani C. Morphometric, hematological and oxidative stress changes in Clarias gariepinus following sub-chronic exposure to tramadol. Com Bio and Phy Part C Tox & Pharm. 2021; 248(4):109096
21. Akhigbe R, Ajayi A. Testicular toxicity following chronic codeine administration is via oxidative DNA damage and up-regulation of NO/TNF-α and caspase 3 activities. PLoS One. 2020;15(3): e0224052. doi: 10.1371/journal.pone.0224052.
22. Younus H. Therapeutic potentials of superoxide dismutase. Int J Health Sci. (Qassim) 2018; 12(3):88-93
23. Dominko K, Dikic D, Hecimovic S. Enhanced activity of superoxide dismutase is a common response to dietary and genetically induced increased cholesterol levels. Nutr Neurosci. 2020;(5):398-410. doi: 10.1080/1028415X.2018.1511027
24. Jiang XY, Chen Q, Chen XY, Sun QY, Jing F, Zhang HQ, Xu J, Li XH, Guan QB. Superoxide dismutases: marker in predicting reduced left ventricular ejection fraction in patients with type 2 diabetes and acute coronary syndrome. BMC Cardiovasc Disord. 2024;24(1):191. doi: 10.1186/s12872-024-03867-2.
25. Nandi A, Yan LJ, Jana CK, Das N. Role of Catalase in Oxidative Stress- and Age-Associated Degenerative Diseases. Oxid Med Cell Longev. 2019; 2019:9613090. doi: 10.1155/2019/9613090.
26. Wróblewska J, Wróblewski M, Hołyńska-Iwan I, Modrzejewska M, Nuszkiewicz J, Wróblewska W, Woźniak A. The Role of Glutathione in Selected Viral Diseases. Antioxi. 2023; 12(7):1325. https://doi.org/10.3390/antiox12071325
27. Lin TH, Rao MY, Lu HW, Chiou CW, Lin ST, Chao HW, Zheng ZL, Cheng HC, Lee TM. A role for glutathione reductase and glutathione in the tolerance of Chlamydomonas reinhardtii to photo-oxidative stress. Physiol Plant. 2018;162(1):35-48. doi:10.1111/ppl.12622
28. Hong KS, Pagan K, Whalen W, Harris R, Yang J, Stout-Delgado H, Cho SJ. The Role of Glutathione Reductase in Influenza Infection. Am J Respir Cell Mol Biol. 2022;67(4):438-445. doi: 10.1165/rcmb.2021-0372OC.
29. Bao YJ, Zhou Q, Yu X, Yu X, Castellino FJ. Analysis and Characterisation of Glutathione Peroxidases in an Environmental Microbiome and Isolated Bacterial Microorganisms. J Microbiol Biotechnol. 2023;33(3):299-309. doi: 10.4014/jmb.2209.09006.
30. Handy DE, Loscalzo J. The role of glutathione peroxidase-1 in health and disease. Free Radic Biol Med. 2022; 188:146-161. doi: 10.1016/j.freeradbiomed.2022.06.004.
31. Chen PK, Yeo KJ, Huang PH, Chang SH, Chang CK, Lan JL, Chen DY. Increased Lipid Peroxidation May Be Linked to Ferritin Levels Elevation in Adult-Onset Still's Disease. Biomed. 2021;9(11):1508. doi: 10.3390/biomedicines9111508.
32. Fu Y, He Y, Phan K, Bhatia S, Pickford R, Wu P, Dzamko N, Halliday GM, Kim WS. Increased unsaturated lipids underlie lipid peroxidation in synucleinopathy brain. Acta Neuropathol Commun. 2022;10(1):165. doi: 10.1186/s40478-022-01469-7.