DOI: 10.69946/ojms/2026.04.01.01, pp(1-10)

The Predictive Role of CYP3A4 and MDA in Duration-Dependent Oxidative and Metabolic Hepatic Alterations among Chronic Methamphetamine Users

Ali Faried Salman[1], Ghid Hassan Abdulhadi[2], Mushtaq Talib Hashim[3],
[1, 2]Department of biochemistry, college of Medicine, University of Baghdad, 11001, Iraq.
[3]Department of Medicine, College of Medicine-University of Baghdad, 11001, Iraq.
Corresponding Author email: ghid.h.ah@comed.uobagdad.edu.iq

Abstract

Background: Methamphetamine (METH) is a powerful psych stimulant that causes hepatotoxic and neurotoxic effects through metabolic disruption and oxidative stress. Despite growing evidence of liver impairment brought on by methamphetamine, it is still unclear how exposure duration affects oxidative markers and cytochrome P450 (CYP3A4) activity.
Objectives: The objective of this study was to determine how long-term methamphetamine usage is associated with liver abnormalities, to find out if long-term exposure makes oxidative and metabolic problems worse, and to determine whether these biochemical changes happen before or at the same time as changes in LFTs, which would explain how methamphetamine causes progressive liver damage.
Methods: A case-control study was performed on 116 male individuals aged 18 to 40 years, including 80 METH users divided into two groups according to the duration of use (G1 3-5 years; n =44 and G2 6-8 years; n = 36) and 36 control participants. Serum CYP3A4, MDA, LFTs, albumin, total protein, and globulin levels were measured.
Results: Age and body mass index did not significantly differ across groups. ($p > 0.05$). CYP3A4 levels were markedly reduced in both METH user groups compared with controls ($p<0.001$) where MDA levels were significantly elevated ($p<0.001$), showing a duration-dependent increase. ALT, AST, and ALP were significantly higher in long-term users ($p<0.05$). While total protein and albumin increased significantly in both groups ($p<0.001$).
Conclusions: Prolonged METH exposure induced progressive oxidative and metabolic hepatic alteration that preceded clinically apparent hepatotoxicity. CYP3A4 inhibition and MDA elevation serve as sensitive early biomarkers for detecting subclinical hepatic impairment in chronic METH users, underscoring their potential value as early diagnostic.
Keywords: Methamphetamine, CYP3A4, oxidative stress, malonaldehyde, liver function test, hepatotoxicity

1. Introduction

Methamphetamine (METH) is a powerful stimulant of the central nervous system (CNS). It is a highly addictive drug that causes abnormal physiological and psychological states [1]. Street ice and crystal meth are other names for amphetamines. METH is one of the four amphetamines that are often used in the US. Dextroamphetamine is added to METH in Iraq [2]. Hepatotoxicity,

DOI: 10.69946/ojms/2026.04.01.01, pp(1-10)

cardiovascular toxicity, and neurotoxicity are among the multi-system toxicities linked to long-term or high-dose METH usage [3]. METH Reactive oxygen species (ROS), oxidative stress-induced aging, apoptosis, and necrosis are among the negative consequences associated with use [4].

When free radicals accumulate, Oxidative stress occurs due to a difference between the generation of oxidants and the capacity of antioxidant defences, which causes crucial macromolecular damage. The term "reactive oxygen species" (ROS) refers to a category of free radicals and reactive species generated from molecular oxygen. These reactive oxygen species cause irreversible damage to macromolecules, such as DNA, proteins, lipids and carbohydrates in the body [5], [6]. Oxidative stress, in particular an increased malondialdehyde (MDA) content (as a marker of lipid peroxidation) as well as a decreased glutathione (GSH) level have been reported to be associated with METH exposure [7]. Enzymes, such as cytochrome P450, are responsible for most of the metabolism of METH in the liver, which leads to active metabolites (amphetamine and 4-hydroxymethamphetamine). After this; it is largely cleared by the kidneys in the urine [8].

Cytochrome P450 (CYP) proteins belong to a family of heme-containing enzymes that play an essential role in the metabolism of many drugs and other xenobiotics. CYP enzymes reside in the endoplasmic reticulum of cells across the body, with greatest abundance in liver. CYP enzymes can facilitate a wide array of processes, encompassing oxidation, reduction, hydrolysis, and isomerization [9]. Among the 57 potentially functional human CYP enzymes, the CYP1, CYP2, and CYP3 families are responsible for the metabolism of over 80% of therapeutically used medicines. CYP-dependent metabolism converts lipophilic substances into water-soluble forms for enhanced excretion and affects treatment outcomes by altering drug efficacy, safety, bioavailability, and resistance in both primary metabolic organs and concentrated drug action sites [10], [11].

Among the CYP isoforms, CYP3A4 has gained significant clinical attention due to its extensive involvement in drug metabolism and distinct regulatory mechanisms. CYP3A4, the most abundant hepatic hormone, is responsible for the metabolism of over 30% of prescribed drugs [12], [13]. CYP3A4 contributes to bile acid detoxification, the termination of steroid hormone action, and the elimination of phytochemicals in food and the majority of medicines [14]. CYP3A4 shows the largest interindividual differences in mRNA and protein expression in the liver, by a factor of several tens to hundreds [15].

There is growing evidence that exposure to methamphetamine induces oxidative stress and disrupts hepatic metabolism. However, the extent to which the use duration influences the development and severity of these alterations remains unclear. Most previous studies have focused on apparent hepatotoxicity using conventional liver function tests without examining early biochemical disturbances, such as cytochrome P450 (CYP3A4) inhibition and lipid peroxidation (reflected by elevated MDA levels), which may precede clinically detectable abnormalities. Furthermore, the potential interactions between these markers and traditional liver function parameters across different exposure durations have not been thoroughly characterized [16], [17].

Therefore, the present study aimed to investigate duration-related hepatic changes linked to long-term METH usage, determine whether extended exposure to METH causes oxidative metabolic disturbance and determine whether changes in liver function tests are preceded or coincident with

DOI: 10.69946/ojms/2026.04.01.01, pp(1-10)

these biochemical changes, thereby elucidating the progressive pattern of hepatic injury caused by METH.

2. Subjects and Methods

2.1 Subject

This case–control study included 80 male methamphetamine users aged 18–40 years. Participants were divided into two groups based on how long they had been using methamphetamine.: Group 1 (G1), 3–5 years (n = 44), and Group 2 (G2), 6–8 years (n = 36). Additionally, a control group of (n = 36) age-matched healthy males (18–40 years) was enrolled.

The inclusion criteria for the METH group were a confirmed diagnosis of METH use disorder by a psychiatrist according to the DSM-5 criteria, a history of chronic METH use, and a positive urine screening test for amphetamines at the time of recruitment. Exclusion criteria for all participants included known pre-existing liver diseases (e.g., hepatitis B and C and cirrhosis), comorbid substance use disorders (except nicotine), HIV infection, current use of medications known to affect cytochrome P450 enzyme activity or liver function, and any chronic medical condition (e.g., diabetes and cardiovascular disease).

Data collection was conducted between January and June 2025. The Al-Qanat Center for Social Rehabilitation in Baghdad, Iraq, provided ethical approval. All procedures were performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants after the study procedure was fully explained (IRB 1068, 12/01/2025).

2.2 Blood sample collection and biochemical analysis

Peripheral blood samples (5 mL) were obtained from each patient and from the control group. Blood samples were separated by centrifugation for 20 minutes at 1000 x g to obtain serum. The separated serum samples were stored in a deep freeze at -20 ℃ until the time of CYP3A4 and MDA measurement.

Serum CYP3A4 levels were measured using sandwich enzyme-linked immunosorbent assay kits (Fine Test, China). MDA concentrations were measured using competitive inhibition enzyme-linked immunosorbent assay (Competitive-ELISA) according to the manufacturer's instructions (Fine Test and ELK, China), respectively.

Routine liver function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total serum bilirubin (TSB), total protein, globulin, and albumin, were assessed on the same day of blood collection to ensure consistency in clinical biochemistry profiling. They were performed using the Beckman Coulter 480 AU Chemistry Analyzer, a diagnostic device from Beckman Coulter Germany. Serum globulin levels were calculated by subtracting the albumin concentration from the total protein concentration (Globulin = Total Protein − Albumin) [18].

2.3 Statistical analysis

Statistical analysis was conducted with Microsoft Excel for data organization and the Statistical Package for the Social Sciences (SPSS) version 27.0. The data are presented as the mean ± standard deviation (SD). Differences between patients and control groups were assessed using Student's t-test.

DOI: 10.69946/ojms/2026.04.01.01, pp(1-10)

The ANOVA test was utilized to compare multiple distinct groups in order to evaluate the differences between the means of numerical data. P-values of <0.001 and <0.05 were deemed very significant and significant, respectively.

3. Results

No significant differences were observed in age or body mass index (BMI) among the three study groups. The mean age was (27.54 ± 6.24) years in participants with G1 of METH use, (32.25 ±3.97) years in those with G2 of METH use, and (30.22 ± 6.41) years in the control group G3. Similarly, the mean BMI values were (23.43 ± 2.81) kg/m², (23.63 ± 2.02) kg/m² and (22.96 ± 2.40) kg/m² for G2, G3, and control groups G3, respectively, as presented in Table 1.

Table 1: Demographic characteristics of the participants

Variable	Control (n = 36) Mean ± SD (G3)	3–5 years (n=44) Mean ± SD (G1)	6–8 years (n=36) Mean ± SD (G2)	p-value (G1)	p-value (G2)
Age (years)	30.22 ± 6.41	27.54 ± 6.24	32.25 ±3.97	0.064	0.112
BMI (kg/m²)	22.96 ± 2.40	23.43 ± 2.81	23.63 ± 2.02	0.422	0.207

As shown in Table 2 and Figs. 1 and 2, CYP3A4 levels were significantly decreased in both G1 and G2 compared with the control group (p <0.0001), while MDA levels were significantly increased (p < 0.0001). ALT and AST showed no significant changes in G1 but were significantly elevated in G2 (p < 0.05). Total protein and albumin levels were significantly higher in both G1 and G2 (p< 0.0001), whereas ALP and globulin increased significantly only in G2. ANOVA revealed significant differences among the groups for most parameters, except for TSB.

Table 2: Mean± (S.D) value of the parameters of healthy controls and groups

Parmeter	Control Mean± (S.D)	G1 Mean± (S.D)	G1 p-value	G2 Mean± (S.D)	G2 p-value	ANOVA
CYP3A4 (pg/mL)	1531±461.7	486.47±176.27	<0.0001**	486.53±187.36	<0.0001**	<0.0001**
MDA (ng/mL)	21.92±1.51	26.78±2.636	<0.0001**	29.05±2.53	<0.0001**	<0.0001**
ALT (U/L)	29.13±8.71	29.75±9.98	0.77	36.4±14.5	0.01*	0.036*
AST (U/L)	23.166±8.32	24.13±10.03	0.63	30.5±14.4	0.01*	0.038*
AST/ALT	0.821±0.27	0.970±0.665	0.18	0.866±0.30	0.518	<0.0001**
TSB (mg/dL)	0.841±0.19	0.816±0.25	0.61	0.899±0.43	0.371	0.253
ALP (U/L)	81.27±14.29	79.5±22.22	0.66	97.72±33.43	0.009*	0.015*
Total protein (g/dL)	6.702±0.36	7.45±0.79	<0.0001**	7.51±0.85	<0.0001**	<0.0001**
Albumin(g/dl)	3.84±0.23	4.48±0.47	<0.0001**	4.30±0.55	<0.0001**	<0.0001**
Globulin (g/dl)	2.85±0.18	2.97±0.77	0.33	3.21±0.68	0.003*	0.025*
A/G	1.35±0.08	1.64±0.56	0.001*	1.399±0.33	0.409	0.003*

*P <0.05 is considered significant.

** P <0.001 is highly significant

DOI: 10.69946/ojms/2026.04.01.01, pp(1-10)

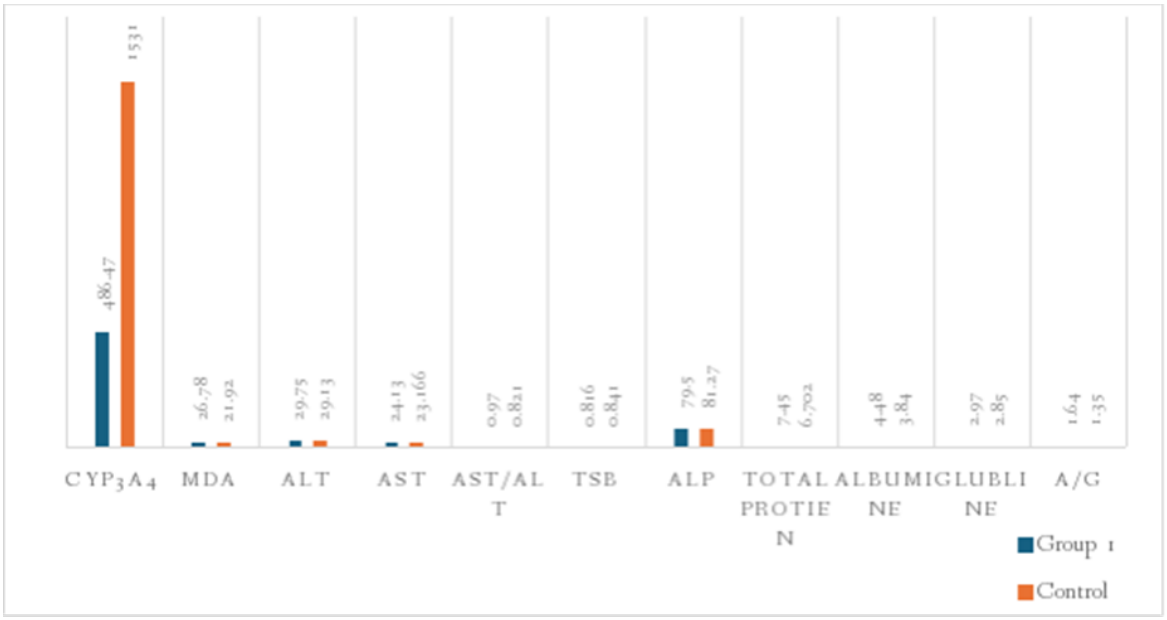

Fig. 1 Serum marker levels between the control and G1 groups.

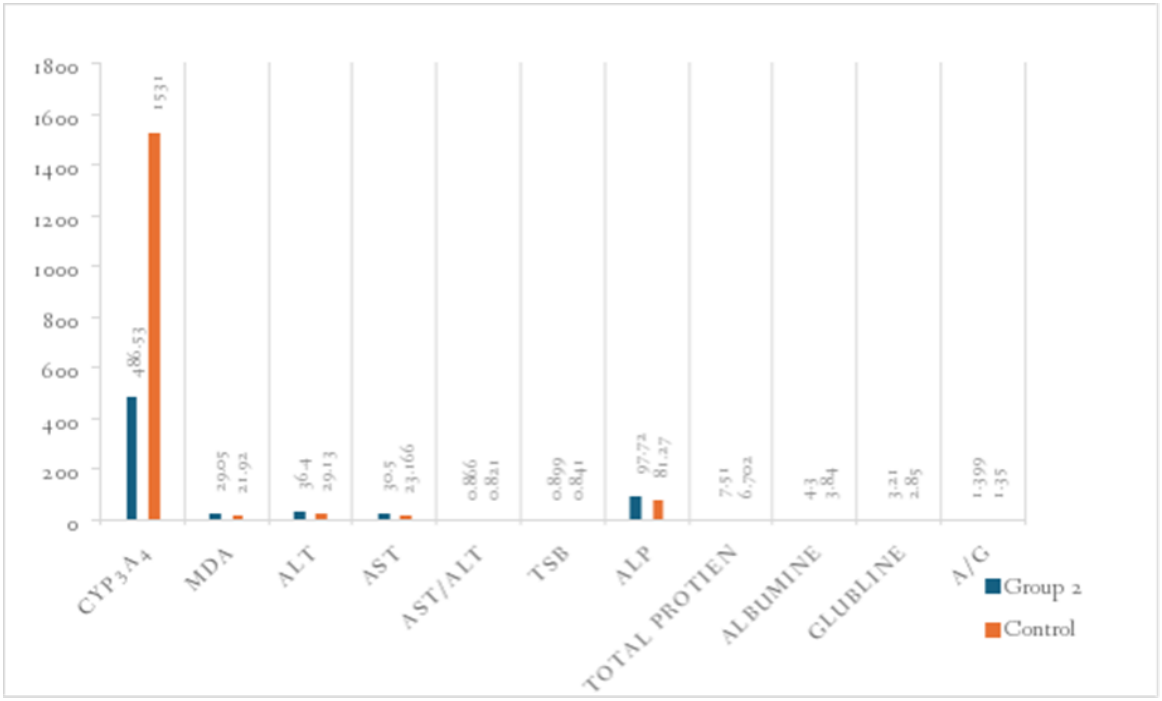

Fig. 2 Serum marker levels between the control and G2 groups

4. Discussion

The present study evaluated CYP3A4 suppression and MDA elevation levels as early predictive biomarkers of methamphetamine-induced hepatic impairment, in conjunction with alterations in conventional liver function tests, providing novel insight into the subclinical progression of METH-related hepatotoxicity.

No significant differences in age or BMI were observed among the three groups. This suggests that baseline demographic characteristics were comparable, indicating that these variables did not confound or influence the studied biochemical markers [19], [20].

DOI: 10.69946/ojms/2026.04.01.01, pp(1-10)

Serum CYP3A4 levels were markedly reduced in both METH user groups compared with controls. However, no significant difference was observed between the short-term (3-5 years) and long-term (6-8 years) METH use groups, indicating that the inhibitory effect of METH on CYP3A4 reaches a plateau after prolonged exposure. This trend indicates that the majority of enzyme inhibition takes place within the first few years of use, which is followed by stabilization. Early loss of the hepatic metabolic function was reported for CYP3A4, a key enzyme responsible for the metabolism of nearly 50%of clinically administered drugs [21]. The down-regulation in expression of the enzyme as detected would imply that prolonged METH exposure may progressively weaken the hepatic enzymatic defense against xenobiotics, thereby predisposing it to drug sequestration, toxicity, and overall metabolism dysfunction. The hepatic microsomal CYP3A4 isoform, which is the most abundant of the cytochrome P450 isoforms in the liver, was significantly lower in users, probably due to mechanisms associated with oxidative stress. ROS are capable of damaging the endoplasmic reticulum in hepatocytes and depleting ATP, which leads to impairment of CYP3A4 synthesis. CYP3A4, moreover, can also be reversibly inhibited by reactive metabolites [22].

Chronic METH use demonstrates the extent of oxidative damage, reflecting significantly higher MDA levels in response to chronic methamphetamine use. MDA levels augmented and gradually increased in both MSG groups, but significantly increased in the long-term use group and were lowest in controls [23]. This pattern reflects the extent of lipid peroxidation and degradation of hepatocyte membrane integrity in prolonged METH exposure. The gradual increase in MDA levels generates robust evidence that METH induces oxidative stress in a time-related manner, overwhelming the cellular antioxidative defense system and provoking progressive hepatic damage. These findings underscore the importance of assessing lipid peroxidation in drug-induced hepatotoxicity research, and indicate that MDA may be an applicable biomarker of oxidative injury in METH abusers [24], [25].

The results of this study are in agreement with Dic-Ijiewere and Osadolor (2023), who reported a significantly elevated MDA level decrease in hepatic CYP3A4 enzyme when alcohol is concurrently used with tramadol, which indicates that oxidative stress plays a critical role in drug-induced hepatotoxicity. These increased MDA and decreased CYP3A4 phenomena are consistent with what was seen in long-term methamphetamine users, suggesting common liver metabolic-oxidative toxicity between some hepatotoxins [26].

In contrast, both user groups levels of albumin and total protein were noticeably higher than those of the control group. Although a mild albumin increase may initially reflect adaptive hepatic responses, chronic elevation could indicate dehydration or altered protein turnover. On the other hand, a significant rise in globulin levels and the altered A/G ratio observed particularly in the 6–8 year group may indicate immune activation secondary to oxidative stress and hepatic inflammation [27], [28]

Regarding liver function parameters, ALT, AST and ALP were significantly increased only for the longer exposure (6–8 years) but kept within the reference limits. These results also indicate a hepatic injury beginning in infancy. Only marginally elevated transaminase levels have been found, in line with the described direct hepatocellular and cytotoxic effect of METH itself [29] and toxicity due to METABs-induced mitochondrial injury.

DOI: 10.69946/ojms/2026.04.01.01, pp(1-10)

Also, Merino de Paz et al. [30] reported that, while classical serum liver enzymes ALT, AST and ALP remained around the normal values, MDA in blood was significantly elevated among IBD patients. They conclude that oxidative stress (as depicted by levels of MDA) is more related to subclinical liver abnormalities and modifications of lipids than the changes in traditional liver function tests.

Our finding is related to this, as the MDA activity as an oxidative and metabolic indicator could reflect incipient hepatic injury in its early stage before any detectable changes can be seen by LFTs. This difference illustrates that clinical normality does not equal statistical significance, even when the levels remain in the reference range. The middle of the range marks the mean and a statistically significant upward deviation from midrange signifies that there is some subclinical dysfunction [30].

Yadav et al. [31], demonstrated that the CYP3A4 enzyme exhibits a time-dependent inactivation mechanism upon exposure to inhibitory compounds, contributing to one of the key pharmacokinetic changes and characteristic interactions. Human liver microsomes (HLMs) have been approved for use, where the enzyme was transfected with several inhibitors, such as troleandomycin, erythromycin, verapamil, and diltiazem, for short periods (up to 60 minutes). However, in a broad reversible study, the numerical model clearly indicates that activation uses a dynamically distinct mechanism, characterized by rapid retraction and a low level of non-contact in the enzyme.

The creation of this pattern has been explained by the use of complexes established between the enzyme and metabolic intermediate complexes that enable it to participate partially, in addition to oxidative compensation that changes the protein structure of the enzyme, making the restart process in liver cells limited but continuous, at the beginning of a marathon with the enzyme plateau phase [31].

In comparison with our findings, the early decline and subsequent stabilization of CYP3A4 levels in methamphetamine users is entirely consistent with this model of temporal inhibition. Chronic use appears to induce a strong and irreversible initial inhibition of the enzyme, followed by a stabilization phase resulting from a balance between oxidative damage and enzyme resynthesis. Our study's early observation of a decline in CYP3A4 activity reflects the TDI mechanism described by Yadav et al., supporting the hypothesis that metabolic damage starts early and levels become stable at a low enzyme activity despite prolonged exposure. Usually, abnormalities in LFTs appear after a longer length of time, but this metabolic decrease becomes apparent earlier [31].

In conclusion, the results indicate long-term methamphetamine users eventually develop a dysfunction of functional liver enzymes despite values remaining within reference ranges. It should be emphasized that this significant increase is indicative of the beginning of subclinical functional impairment. The study also stresses that CYP3A4 and MDA display early metabolic and oxidative changes, which are much prior to any obvious alterations in routine liver functional tests, thereby being of remarkable value to be used as early metabolic assay for diagnosis of the liver injury at its progressive phase (especially among chronic users). This underscores the importance of these lines in early detection and prevention of meth-induced hepatotoxicity. Extensive studies have focused on uncovering mechanisms involved in meth metabolism.

DOI: 10.69946/ojms/2026.04.01.01, pp(1-10)

5. Recommendations

CYP3A4 and MDA are proposed as early markers for the detection of meth-induced hepatic injury because they reflect functional disturbances before conventional liver enzyme changes. In chronic users, it would be more preferable for them to be included in standard screening to stage hepatotoxicity early. The incorporation of both of these markers in treatment and prevention follow-up protocols is also suggested so that drug therapy can be adapted and targeted toward decreasing hepatic oxidative stress.

References

[1] Kotajima-Murakami, H., Takano, A., Hirakawa, S., Ogai, Y., Funada, D., Tanibuchi, Y., Ban, E., Kikuchi, M., Tachimori, H., Maruo, K., Kawashima, T., Tomo, Y., Sasaki, T., Oi, H., Matsumoto, T., & Ikeda, K. (2022). Ifenprodil for the treatment of methamphetamine use disorder: An exploratory, randomized, double-blind, placebo-controlled trial. Neuropsychopharmacology Reports, 42(1), 92–104. https://doi.org/10.1002/npr2.12232.

[2] Abbass, M., Al-Hemiary, N., & Sahib, H. B. (2024). The impact of methamphetamine on psychosocial variables in patients from Iraq. Frontiers in Psychiatry, 15, 1376636. https://doi.org/10.3389/fpsyt.2024.1376636.

[3] Jayanthi, S., Daiwile, A. P., & Cadet, J. L. (2021). Neurotoxicity of methamphetamine: Main effects and mechanisms. Experimental Neurology, 344, 113795. https://doi.org/10.1016/j.expneurol.2021.113795

[4] Korthuis, P. T., Cook, R. R., Foot, C. A., Leichtling, G., Tsui, J. I., Stopka, T. J., ... Young, A. M. (2022). Association of methamphetamine and opioid use with nonfatal overdose in rural communities. JAMA Network Open, 5(8), e2226544. https://doi.org/10.1001/jamanetworkopen.2022.26544.

[5] Hao, Y., Xing, M., & Gu, X. (2021). Research progress on oxidative stress and its nutritional regulation strategies in pigs. Animals, 11(5), 1384. https://doi.org/10.3390/ani11051384.

[6] Yadav, D. M., Niculescu, A. G., Lungu, I. I., Radu, C. I., Vladâcenco, O., Roza, E., Costăchescu, B., Grumezescu, A. M., & Teleanu, R. I. (2022). An overview of oxidative stress, neuroinflammation, and neurodegenerative diseases. International Journal of Molecular Sciences, 23(11), 5938. https://doi.org/10.3390/ijms23115938.

[7] Ramli, F. F., Rejeki, P. S., Ibrahim, N., Abdullayeva, G., & Halim, S. (2025). A mechanistic review on toxicity effects of methamphetamine. International Journal of Medical Sciences, 22(3), 482–507. https://doi.org/10.7150/ijms.99159.

[8] Cajanding, R. J. M. (2019). MDMA-associated liver toxicity: Pathophysiology, management, and current state of knowledge. AACN Advanced Critical Care, 30(3), 232–248. https://doi.org/10.4037/aacnacc2019852.

[9] Zhao, M., Ma, J., Li, M., Zhang, Y., Jiang, B., Zhao, X., et al. (2021). Cytochrome P450 enzymes and drug metabolism in humans. International Journal of Molecular Sciences, 22(23), 12808. https://doi.org/10.3390/ijms222312808.

[10] Guengerich, F. P. (2021). A history of the roles of cytochrome P450 enzymes in the toxicity of drugs. Toxicological Research, 37(1), 1–23. https://doi.org/10.1007/s43188-020-00056-z.

[11] Danielson, P. Å. (2002). The cytochrome P450 superfamily: Biochemistry, evolution and drug metabolism in humans. Current Drug Metabolism, 3(6), 561–597. https://doi.org/10.2174/1389200023337054.

[12] Zhang, X., Guo, J., Cheng, F., & Li, S. (2021). Cytochrome P450 enzymes in fungal natural product biosynthesis. Natural Product Reports, 38(6), 1072–1099. https://doi.org/10.1039/D1NP00004G

[13] Kinter, L. B., DeHaven, R., Johnson, D. K., & DeGeorge, J. J. (2021). A brief history of use of animals in biomedical research and perspective on non-animal alternatives. ILAR Journal, 62(1–2), 7–16. https://doi.org/10.1093/ilar/ilab020.

[14] Tu, D.-Z., Hu, X.-Y., Lei, J.-X., Liu, S.-Y., Xiao, Z.-P., Yang, L., et al. (2025). A patent review of CYP3A4 inhibitors (2018–present). Expert Opinion on Therapeutic Patents, 35(5), 503–513. https://doi.org/10.3390/pharmaceutics13081268.

[15] Kondža, M., Bojić, M., Tomić, I., Maleš, Ž., Rezić, V., & Ćavar, I. (2021). Characterization of the CYP3A4 enzyme inhibition potential of selected flavonoids. Molecules, 26(10), 3018.

[16] Sami, S. W., & Mahmood, H. G. (2025). Laminin levels as a biomarker for liver injury in methamphetamine addict. Journal of the Faculty of Medicine Baghdad, 67(1), 104–109. https://doi.org/10.32007/jfacmedbaghdad2477.

[17] Solhi, H., Malekirad, A., Kazemifar, A. M., & Sharifi, F. (2014). Oxidative stress and lipid peroxidation in prolonged users of methamphetamine. Drug Metabolism Letters, 7(2), 79–82. https://doi.org/10.2174/1872312807021405201913 24.

[18] Burtis, C. A., Ashwood, E. R., & Bruns, D. E. (2018). Tietz textbook of clinical chemistry and molecular diagnostics (6th Ed.). Elsevier.

[19] Si, Z., Yang, G., Wang, X., Yu, Z., Pang, Q., Zhang, S. Yu, L. (2023). An unconventional cancer-promoting function of methamphetamine in hepatocellular carcinoma. Life Science Alliance, 6(3), e202201660. https://doi.org/10.26508/lsa.202201660.

[20] Nakama, H., Chang, L., Fein, G., Shimotsu, R., Jiang, C. S., & Ernst, T. (2011). Methamphetamine users show greater than normal age-related cortical gray matter loss. Addiction, 106(8), 1474–1483. https://doi.org/10.1111/j.1360-0443.2011.03433.

[21] Hossam Abdelmonem, B., Abdelaal, N. M., Anwer, E. K. E., Rashwan, A. A., Hussein, M. A., Ahmed, Y. F., et al. (2024). Decoding the role of CYP450 enzymes in metabolism and disease: A comprehensive review. Biomedicines, 12.

[22] Zanger, U. M., & Schwab, M. (2013). Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacology & Therapeutics, 138(1), 103–141. https://doi.org/10.1016/j.pharmthera.2012.12.007.

[23] Zhou, S., Cheng, K., Peng, Y., Liu, Y., Hu, Q., Zeng, S., et al. (2024). Regulation mechanism of endoplasmic reticulum stress on metabolic enzymes in liver diseases. Pharmacological Research, 207, 107332. https://doi.org/10.1016/j.phrs.2023.107332.

[24] Loftis, J. M., & Janowsky, A. (2014). Neuroimmune basis of methamphetamine toxicity. International Review of Neurobiology, 118, 165–197. https://doi.org/10.1016/B978-0-12-801284-0.00007-8

[25] Nookala, A. R., Li, J., Ande, A., Wang, L., Vaidya, N. K., Li, W., et al. (2016). Effect of methamphetamine on spectral binding, ligand docking and metabolism of anti-HIV drugs with CYP3A4. PLOS ONE, 11(1), e0146529. https://doi.org/10.1371/journal.pone.0146529.

[26] Dic-Ijiewere, E. O., & Osadolor, H. B. (2023). CYP24A1 and CYP3A4 levels, renal, hepatic changes, and incidence of oxidative stress in tramadol-alcohol concomitant misuse. Cureus, 15(3), e36877. https://doi.org/10.7759/cureus.36877.

[27] Xu, Q., Wang, J., Li, H., & Chen, X. (2024). A study investigating how the albumin–globulin ratio relates to depression risk within U.S. adults: A cross-sectional analysis. Frontiers in Nutrition, 11, 1453044. https://doi.org/10.3389/fnut.2024.1453044.

[28] Alhalwani, A. Y., Khan, M. A., Bahadur, R. Y., Almalki, H. A., & Sannan, N. S. (2023). Assessment of globulin levels and albumin-to-globulin ratio in patients with type 2 diabetes and retinopathy: A retrospective single-center study. The Open Ophthalmology Journal, 17(1).

[29] Mohammed, N. S., Ali, Z. Q., Mohamed, A. S., & Mirza, S. A. (2024). The impact of methamphetamine on liver injury in Iraqi male addicts. Toxicology Reports, 13, 101806.

[30] Merino de Paz, N., Carrillo-Palau, M., Hernández-Camba, A., Abreu-González, P., de Vera-González, A., González-Delgado, A. Ferraz-Amaro, I. (2024). Association of serum malонdialdehyde levels with lipid

profile and liver function in patients with inflammatory bowel disease. Antioxidants, 13(10), 1171. https://doi.org/10.3390/antiox13101171.

[31] Yadav, J., Korzekwa, K., & Nagar, S. (2018). Improved predictions of drug–drug interactions mediated by time-dependent inhibition of CYP3A. Molecular Pharmaceutics, 15(5), 1979–1995. https://doi.org/10.1021/acs.molpharmaceut.7b01011.