

Combined Chemical Exposures and Synergistic Toxicity: Unraveling Biochemical Interactions in the Anthropocene

Kungu Erisa

Faculty of Pharmacy Kampala International University Uganda

Email: erisa.kungu@studwc.kiu.ac.ug

ABSTRACT

Human and ecological systems in the Anthropocene are exposed to complex mixtures of chemicals from industrial, agricultural, pharmaceutical, and consumer-product sources. These combined exposures frequently produce effects that are not predicted by single-chemical toxicology: interactions can be additive, antagonistic, or synergistic, with synergy posing the greatest concern because low-level co-exposures may produce unexpectedly large adverse outcomes. This review synthesizes mechanistic knowledge of mixture toxicity with an emphasis on biochemical interactions that drive synergy. We examine key interaction modalities - competitive and noncompetitive enzyme inhibition, receptor co-activation and cross-talk, redox cycling and oxidative stress amplification, disruption of detoxification pathways and transporters, endocrine network interference, and microbiome-mediated biotransformation. Methods for assessing mixture effects are evaluated, including experimental designs (fixed-ratio and factorial mixtures), dose-response modelling (concentration addition, independent action, response-surface methods, isobolograms), and emerging in vitro, in vivo, and in silico tools (high-throughput screening, organoids, PBPK-toxicodynamic models, systems toxicology). We discuss biomarkers and multi-omics strategies for detecting synergistic biochemical perturbations and highlight illustrative case examples where co-exposures intensify risk (e.g., pesticide combinations, metal-organic pollutant interactions, polypharmacy and environmental contaminants). Critical challenges are identified: exposure characterization, realistic dose metrics, non-monotonic and low-dose effects, interindividual variability, and regulatory frameworks that still largely rely on single-chemical assessment. The review concludes with research priorities to improve prediction and prevention of synergistic toxicity, advocating integrated experimental-computational pipelines, standardized mixture reference materials, human-relevant models, and policy adaptations that account for cumulative and interaction-driven risks.

Keywords: mixture toxicity, synergy, oxidative stress, pharmacokinetic interactions, systems toxicology

INTRODUCTION

In the modern Anthropocene era, environmental chemical exposures are rarely confined to a single compound [1-4]. Instead, humans, animals, and ecosystems are increasingly subjected to complex mixtures of pollutants originating from industrial emissions, agricultural runoff, pharmaceutical residues, consumer products, and natural transformation products. These chemical cocktails permeate air, water, soil, and food chains, creating a pervasive background of chronic, low-dose exposures [5-9]. Common examples include simultaneous contact with pesticides, heavy metals, polycyclic aromatic hydrocarbons, flame retardants, and microplastic-associated contaminants. Traditional toxicological frameworks and regulatory guidelines have primarily focused on assessing individual chemicals in isolation [10-13]. While this approach has provided valuable insights into dose-response relationships, it fails to capture the realities of combined exposures. Mounting evidence indicates that chemicals rarely act independently; instead, their interactions can alter toxic outcomes in ways that are qualitatively and quantitatively distinct [14-17]. These combined effects may be additive, antagonistic, or synergistic. Of greatest concern are synergistic interactions, in which the joint effect is significantly greater than the sum of individual toxicities. Such

interactions imply that low-level exposures previously regarded as safe may produce unexpected and amplified health risks [18-21]. Understanding the mechanisms that drive synergistic toxicity is essential for modern environmental health sciences [22-26]. This review, therefore examines the biochemical and molecular bases of chemical interactions, highlights experimental and computational methods for assessing mixture effects, and evaluates their implications for risk assessment and policy. By integrating mechanistic insights with real-world exposure scenarios, we aim to clarify the growing challenge of mixture toxicity in human and ecological health.

2. Definitions and Conceptual Framework

The study of combined chemical exposures requires a clear understanding of how mixture effects are defined and classified [27-29]. Traditionally, toxicological interactions are described in relation to the concept of additivity, which serves as the baseline expectation for combined effects. An additive outcome occurs when two or more chemicals act independently but contribute to the same biological response in a manner equal to the sum of their individual effects [30-37]. For example, two pesticides that reduce enzyme activity by 20% each would be expected, under additivity, to produce a 40% reduction when combined. When the combined response is less than predicted by additivity, the interaction is termed antagonistic [38-43]. Antagonism can arise when one compound blocks the uptake, metabolism, or receptor binding of another, effectively diminishing its toxic impact. Conversely, synergy refers to a supra-additive interaction in which the combined effect exceeds the expected sum, often producing disproportionately severe outcomes. Synergistic effects are particularly important because they can emerge even at exposure levels deemed safe for individual chemicals [44-49]. Mechanistically, such interactions can occur at multiple biological levels, including absorption, distribution, metabolism, and excretion (ADME), as well as at intracellular targets, receptor cross-talk pathways, or compensatory physiological systems [50-54]. Importantly, it is necessary to distinguish true biochemical synergy arising from interactive molecular or cellular mechanisms from pharmacokinetic (PK) interactions, where co-exposures alter internal dose distribution [55-59]. Both can yield enhanced toxicity, yet they require different investigative and regulatory approaches. This conceptual framework forms the foundation for assessing the risks posed by real-world chemical mixtures.

3. Mechanisms Driving Synergistic Biochemical Toxicity

Understanding how chemical mixtures produce synergistic toxicity requires examining both pharmacokinetic and pharmacodynamic interactions across multiple biological levels [60-64]. Synergy arises when co-exposures interact in ways that amplify adverse effects beyond what would be predicted from individual chemical toxicity [65-69]. The following mechanisms highlight the principal biochemical pathways through which synergistic effects manifest.

3.1 Pharmacokinetic interactions: altered internal dose

Mixtures can substantially influence absorption, distribution, metabolism, and excretion (ADME), thereby changing internal concentrations of one or more chemicals [70-74]. For instance, one compound may inhibit cytochrome P450 enzymes responsible for metabolizing another xenobiotic, leading to prolonged tissue residence time and increased bioavailability of the toxicant [75-79]. Similarly, competition for transporters or altered renal elimination can enhance systemic exposure. These pharmacokinetic modifications effectively raise the internal dose, increasing the likelihood of downstream biochemical damage even when individual chemicals are present at sub-toxic concentrations.

3.2 Enzyme inhibition and metabolic overload

Direct inhibition of key metabolic enzymes by one compound can prevent detoxification of co-exposed chemicals, resulting in accumulation of reactive intermediates [80-84]. Conversely, induction of bioactivation pathways may increase the production of electrophilic metabolites. When multiple xenobiotics rely on shared conjugation pathways such as glucuronidation, sulfation, or glutathione conjugation, the detoxification system may become overwhelmed, amplifying oxidative stress and covalent protein or DNA damage [85-90]. This metabolic overload is a critical contributor to synergistic toxicity.

3.3 Redox cycling, pro-oxidant amplification, and mitochondrial disruption

Several chemicals generate reactive oxygen species (ROS) through redox cycling or mitochondrial interference. Co-exposures that simultaneously generate ROS and impair antioxidant defenses, such as glutathione depletion or inhibition of superoxide dismutase, can cause exponential increases in oxidative stress [91-94]. Elevated ROS levels trigger lipid peroxidation, protein carbonylation, and mitochondrial dysfunction, creating feed-forward cycles that sensitize cells to apoptosis or necrosis [90].

3.4 Receptor co-activation and signaling cross-talk

Chemicals targeting hormonal, nuclear, or membrane receptors can produce non-linear effects through co-binding, receptor cross-talk, or amplification of downstream transcriptional networks [21]. Endocrine-active chemicals with distinct receptor specificities may converge on shared gene programs controlling development, metabolism, or stress responses, generating synergistic dysregulation that would not be anticipated from single-compound exposures.

3.5 Transporter and barrier interactions

Disruption of barrier integrity-intestinal, blood-brain, or placental-by one chemical can enhance penetration of others [22]. Competition for efflux transporters, including P-glycoprotein and multidrug resistance-associated

proteins (MRPs), can increase intracellular retention of toxicants. These transporter-mediated effects are central to many pharmacokinetic synergies, particularly in organs susceptible to cumulative toxicity [23].

3.6 Microbiome-mediated biotransformation

The gut and environmental microbiomes play a pivotal role in xenobiotic metabolism, sometimes generating more toxic metabolites than the parent compounds. Co-exposures that perturb microbial community composition can alter metabolic outputs, either increasing the formation of harmful metabolites or reducing detoxification capacity [24]. This emergent toxicity illustrates how microbial-mediated interactions may create synergistic effects not predictable from the properties of individual chemicals [25]. Together, these mechanisms illustrate the multifaceted ways in which chemical mixtures interact to produce supra-additive toxic outcomes, underscoring the complexity of assessing real-world exposures in both humans and ecosystems.

4. Methods to Assess Mixture Toxicity

Evaluating the toxicological effects of chemical mixtures requires a combination of experimental and computational strategies that can capture complex interactions.

4.1 Experimental designs

Several experimental approaches are widely used to study mixture toxicity. Fixed-ratio mixture studies involve combining chemicals at predefined proportional concentrations, allowing assessment of additive, synergistic, or antagonistic effects across a range of doses [26]. Factorial designs expand this concept by testing multiple combinations and concentrations simultaneously, providing insights into interaction patterns and dose dependencies. Concentration–response matrices can visualize how changes in the dose of one chemical influence the effect of another, while dose–response surfaces and isobolograms help quantify and interpret deviations from expected additivity [27]. High-throughput combinatorial screening further enables exploration of large chemical spaces, providing rapid mechanistic and phenotypic data for prioritizing mixtures of concern.

4.2 Dose–response modelling

Interpreting mixture effects relies on conceptual frameworks such as concentration addition (CA), which assumes chemicals act via similar mechanisms, and independent action (IA), which assumes dissimilar mechanisms [28]. Deviations from these models indicate interaction. Quantitative approaches—including response-surface modeling, generalized linear models, and statistical interaction terms—allow estimation of synergy or antagonism [29]. Mechanistic pharmacokinetic–pharmacodynamic (PK–PD) models and physiologically based pharmacokinetic (PBPK) frameworks help separate contributions of altered internal dose from intrinsic pharmacodynamic interactions, providing mechanistic insight into observed supra-additive effects.

4.3 In vitro and in silico advances

Modern tools complement traditional studies. High-content cell assays, organoids, and microphysiological systems capture complex tissue-level responses and mechanistic perturbations [30]. Transcriptomic, proteomic, and metabolomic readouts provide systems-level information on affected pathways [31]. In silico approaches, including quantitative structure–activity relationship (QSAR) modeling, machine learning, and network-based systems toxicology, support prediction of potential interactions, prioritize mixtures for experimental testing, and inform regulatory and risk-assessment decisions [32].

CONCLUSIONS

Synergistic toxicity from combined chemical exposures is a defining challenge of the Anthropocene. Mechanistic understanding of PK and PD interactions, coupled with modern experimental and computational tools, can improve prediction and management of mixture risks. Protecting public and environmental health requires shifting from single-chemical paradigms toward integrated assessments that acknowledge interaction-driven hazards and adapt regulation accordingly.

REFERENCES

1. Landrigan PJ, Stegeman JJ, Fleming LE, Allemann D, Anderson DM, Backer LC, Brucker-Davis F, Chevalier N, Corra L, Czerucka D, Bottein MD, Demeneix B, Depledge M, Deheyn DD, Dorman CJ, Fénichel P, Fisher S, Gaill F, Galgani F, Gaze WH, Giuliano L, Grandjean P, Hahn ME, Hamdoun A, Hess P, Judson B, Laborde A, McGlade J, Mu J, Mustapha A, Neira M, Noble RT, Pedrotti ML, Reddy C, Rocklöv J, Scharler UM, Shanmugam H, Taghian G, van de Water JAJM, Vezzulli L, Weihe P, Zeka A, Raps H, Rampal P. Human Health and Ocean Pollution. *Ann Glob Health*. 2020 Dec 3;86(1):151. doi: 10.5334/aogh.2831. PMID: 33354517; PMCID: PMC7731724.
2. Alum, E. U. (2025). The role of toxicology in climate change: Understanding the risks of novel environmental toxins. *Sustainable Environment*, 11(1). <https://doi.org/10.1080/27658511.2025.2467485>
3. Oladipo HJ, Tajudeen YA, Taiwo EO, Muili AO, Yusuf RO, Jimoh SA, Oladipo MK, Oladunjoye IO, Egbewande OM, Sodiq YI, et al. Global Environmental Health Impacts of Rare Earth Metals: Insights for Research and Policy Making in Africa. *Challenges*. 2023; 14(2):20. <https://doi.org/10.3390/challe14020020>
4. Payne-Sturges DC, Taiwo TK, Ellickson K, Mullen H, Tchangalova N, Anderko L, Chen A, Swanson M. Disparities in Toxic Chemical Exposures and Associated Neurodevelopmental Outcomes: A Scoping

- Review and Systematic Evidence Map of the Epidemiological Literature. *Environ Health Perspect.* 2023 Sep;131(9):96001. doi: 10.1289/EHP11750. Epub 2023 Sep 27. PMID: 37754677; PMCID: PMC10525348.
5. Ogbodo, John Onyebuchi, Egba, Simeon Ikechukwu., Ogbodo, Chizaramekpere Grace., Onwurah Ikechukwu, Emmanuel and Njoku, Obioma Uzoma. Effects of Exposure to Volatile Organic Compounds (VOCS) Content From Paint on Automobile Paint Workers in Nsukka, South Eastern Nigeria. *Heliyon* 2024; 10(17) e37015
 6. Sprinkle, R.H., Payne-Sturges, D.C. Mixture toxicity, cumulative risk, and environmental justice in United States federal policy, 1980–2016. *Environ Health* 20, 104 (2021). <https://doi.org/10.1186/s12940-021-00764-5>
 7. Schneider, S., Fussell, K.C., Melching-Kollmuss, S. *et al.* Investigations on the dose–response relationship of combined exposure to low doses of three anti-androgens in Wistar rats. *Arch Toxicol* 91, 3961–3989 (2017). <https://doi.org/10.1007/s00204-017-2053-3>
 8. Fajkić A, Lepara O, Jahić R, Hadžović-Džuvo A, Belančić A, Chupin A, Pavković D, Sher EK. Ultra-Processed Diets and Endocrine Disruption, Explanation of Missing Link in Rising Cancer Incidence Among Young Adults. *Cancers.* 2025; 17(13):2196. <https://doi.org/10.3390/cancers17132196>
 9. Rodea-Palomares I, González-Pleiter M, Martín-Betancor K, Rosal R, Fernández-Piñas F. Additivity and Interactions in Ecotoxicity of Pollutant Mixtures: Some Patterns, Conclusions, and Open Questions. *Toxics.* 2015; 3(4):342-369. <https://doi.org/10.3390/toxics3040342>
 10. Cattaneo I, Kalian AD, Di Nicola MR, Dujardin B, Levorato S, Mohimont L, Nathanail AV, Carnessechi E, Astuto MC, Tarazona JV, Kass GEN, Liem AKD, Robinson T, Manini P, Hogstrand C, Price PS, Dorne JLCM. Risk Assessment of Combined Exposure to Multiple Chemicals at the European Food Safety Authority: Principles, Guidance Documents, Applications and Future Challenges. *Toxins (Basel).* 2023 Jan 4;15(1):40. doi: 10.3390/toxins15010040. PMID: 36668860; PMCID: PMC9861867.
 11. Luo, L., Hudson, L.G., Lewis, J. *et al.* Two-step approach for assessing the health effects of environmental chemical mixtures: application to simulated datasets and real data from the Navajo Birth Cohort Study. *Environ Health* 18, 46 (2019). <https://doi.org/10.1186/s12940-019-0482-6>
 12. Sarigiannis, D.A., Hansen, U. Considering the cumulative risk of mixtures of chemicals – A challenge for policy makers. *Environ Health* 11 (Suppl 1), S18 (2012). <https://doi.org/10.1186/1476-069X-11-S1-S18>
 13. Posthuma, L., Altenburger, R., Backhaus, T. *et al.* Improved component-based methods for mixture risk assessment are key to characterize complex chemical pollution in surface waters. *Environ Sci Eur* 31, 70 (2019). <https://doi.org/10.1186/s12302-019-0246-5>
 14. Kassotis CD, Phillips AL. Complex Mixtures and Multiple Stressors: Evaluating Combined Chemical Exposures and Cumulative Toxicity. *Toxics.* 2023; 11(6):487. <https://doi.org/10.3390/toxics11060487>
 15. Tibbitts J, Canter D, Graff R, Smith A, Khawli LA. Key factors influencing ADME properties of therapeutic proteins: A need for ADME characterization in drug discovery and development. *MABs.* 2016;8(2):229-45. doi: 10.1080/19420862.2015.1115937. Epub 2015 Dec 4. PMID: 26636901; PMCID: PMC4966629.
 16. Stielow M, Witczyńska A, Kubryń N, Fijałkowski Ł, Nowaczyk J, Nowaczyk A. The Bioavailability of Drugs—The Current State of Knowledge. *Molecules.* 2023; 28(24):8038. <https://doi.org/10.3390/molecules28248038>
 17. Wu K, Kwon SH, Zhou X, Fuller C, Wang X, Vadgama J, Wu Y. Overcoming Challenges in Small-Molecule Drug Bioavailability: A Review of Key Factors and Approaches. *International Journal of Molecular Sciences.* 2024; 25(23):13121. <https://doi.org/10.3390/ijms252313121>
 18. Hughes TB, Flynn N, Dang NL, Swamidass SJ. Modeling the Bioactivation and Subsequent Reactivity of Drugs. *Chem Res Toxicol.* 2021 Feb 15;34(2):584-600. doi: 10.1021/acs.chemrestox.0c00417. Epub 2021 Jan 26. PMID: 33496184; PMCID: PMC8716317.
 19. Zhang Q, Pi J, Woods CG, Andersen ME. Phase I to II cross-induction of xenobiotic metabolizing enzymes: a feedforward control mechanism for potential hormetic responses. *Toxicol Appl Pharmacol.* 2009 Jun 15;237(3):345-56. doi: 10.1016/j.taap.2009.04.005. Epub 2009 Apr 14. PMID: 19371757; PMCID: PMC2696203.
 20. Alum, E.U., Uti, D.E. & Offor, C.E. Redox Signaling Disruption and Antioxidants in Toxicology: From Precision Therapy to Potential Hazards. *Cell Biochem Biophys* (2025). <https://doi.org/10.1007/s12013-025-01846-8>
 21. Donato MT, Tolosa L. High-Content Screening for the Detection of Drug-Induced Oxidative Stress in Liver Cells. *Antioxidants.* 2021; 10(1):106. <https://doi.org/10.3390/antiox10010106>
 22. Tetel MJ. Nuclear receptor coactivators: essential players for steroid hormone action in the brain and in behaviour. *J Neuroendocrinol.* 2009 Mar;21(4):229-37. doi: 10.1111/j.1365-2826.2009.01827.x. PMID: 19207820; PMCID: PMC2696805.

23. Combarous Y, Nguyen TMD. Membrane Hormone Receptors and Their Signaling Pathways as Targets for Endocrine Disruptors. *J Xenobiot.* 2022 Mar 25;12(2):64-73. doi: 10.3390/jox12020007. PMID: 35466213; PMCID: PMC9036253.
24. Jafari H, Hussain S, Campbell MJ. Nuclear Receptor Coregulators in Hormone-Dependent Cancers. *Cancers.* 2022; 14(10):2402. <https://doi.org/10.3390/cancers14102402>
25. Sas, L., Lardon, F., Vermeulen, P.B. *et al.* The interaction between ER and NFkB in resistance to endocrine therapy. *Breast Cancer Res* 14, 212 (2012). <https://doi.org/10.1186/bcr3196>
26. Jeon, S., Jeon, Y., Lim, JY. *et al.* Emerging regulatory mechanisms and functions of biomolecular condensates: implications for therapeutic targets. *Sig Transduct Target Ther* 10, 4 (2025). <https://doi.org/10.1038/s41392-024-02070-1>
27. Bloch D, Diel P, Epe B, Hellwig M, Lampen A, Mally A, Marko D, Villar Fernández MA, Guth S, Roth A, Marchan R, Ghallab A, Cadenas C, Nell P, Vartak N, van Thriel C, Luch A, Schmeisser S, Herzler M, Landsiedel R, Leist M, Marx-Stoelting P, Tralau T, Hengstler JG. Basic concepts of mixture toxicity and relevance for risk evaluation and regulation. *Arch Toxicol.* 2023 Nov;97(11):3005-3017. doi: 10.1007/s00204-023-03565-6. Epub 2023 Aug 24. PMID: 37615677; PMCID: PMC10504116.
28. Kortenkamp A. Ten years of mixing cocktails: a review of combination effects of endocrine-disrupting chemicals. *Environ Health Perspect.* 2007 Dec;115 Suppl 1(Suppl 1):98-105. doi: 10.1289/ehp.9357. PMID: 18174957; PMCID: PMC2174407.
29. Cedergreen, N., Pedersen, K.E. & Fredensborg, B.L. Quantifying synergistic interactions: a meta-analysis of joint effects of chemical and parasitic stressors. *Sci Rep* 13, 13641 (2023). <https://doi.org/10.1038/s41598-023-40847-6>
30. Limbu S, Glasgow E, Block T, Dakshanamurthy S. A Machine-Learning-Driven Pathophysiology-Based New Approach Method for the Dose-Dependent Assessment of Hazardous Chemical Mixtures and Experimental Validations. *Toxics.* 2024; 12(7):481. <https://doi.org/10.3390/toxics12070481>
31. Alum, E.U., Manjula, V.S., Uti, D.E., Echegu, D.A., Ugwu, O.P.C., Egba, S.I., Agu, P.C. (2025). Metabolomics-Driven Standardization of Herbal Medicine: Advances, Applications, and Sustainability Considerations. *Natural Product Communications.* 2025;20(8). doi:10.1177/1934578X251367650
32. Raza A, Salehi H, Bashir S, Tabassum J, Jamla M, Charagh S, Barmukh R, Mir RA, Bhat BA, Javed MA, Guan DX, Mir RR, Siddique KHM, Varshney RK. Transcriptomics, proteomics, and metabolomics interventions prompt crop improvement against metal(loid) toxicity. *Plant Cell Rep.* 2024 Feb 27;43(3):80. doi: 10.1007/s00299-024-03153-7. PMID: 38411713; PMCID: PMC10899315.
33. Okon MB, Ugwu OP, Ugwu CN, Ogenyi FC, Swase DT, Anyanwu CN, Eze VH, Ugwu JN, Akinola SA, Mujinya R, Anyanwu EG. From pandemics to preparedness: harnessing AI, CRISPR, and synthetic biology to counter biosecurity threats. *Frontiers in Public Health.* 2025 Nov 26;13:1711344.
34. Ugwu OP, Ogenyi FC, Ugwu CN, Basajja M, Okon MB. Mitochondrial stress bridge: Could muscle-derived extracellular vesicles be the missing link between sarcopenia, insulin resistance, and chemotherapy-induced cardiotoxicity?. *Biomedicine & Pharmacotherapy.* 2025 Dec 1;193:118814.
35. Annamalai A, Tek C. An overview of diabetes management in schizophrenia patients: office based strategies for primary care practitioners and endocrinologists. *International journal of endocrinology.* 2015;2015(1):969182.
36. Kremers SH, Wild SH, Elders PJ, Beulens JW, Campbell DJ, Pouwer F, Lindekilde N, de Wit M, Lloyd C, Rutters F. The role of mental disorders in precision medicine for diabetes: a narrative review. *Diabetologia.* 2022 Nov;65(11):1895-906.
37. Ugwu CN, Ugwu OP, Alum EU, Eze VH, Basajja M, Ugwu JN, Ogenyi FC, Ejemot-Nwadiaro RI, Okon MB, Egba SI, Uti DE. Sustainable development goals (SDGs) and resilient healthcare systems: Addressing medicine and public health challenges in conflict zones. *Medicine.* 2025 Feb 14;104(7):e41535.
38. Ongesa TN, Ugwu OP, Ugwu CN, Alum EU, Eze VH, Basajja M, Ugwu JN, Ogenyi FC, Okon MB, Ejemot-Nwadiaro RI. Optimizing emergency response systems in urban health crises: A project management approach to public health preparedness and response. *Medicine.* 2025 Jan 17;104(3):e41279.
39. Ugwu CN, Ugwu OP, Alum EU, Eze VH, Basajja M, Ugwu JN, Ogenyi FC, Ejemot-Nwadiaro RI, Okon MB, Egba SI, Uti DE. Medical preparedness for bioterrorism and chemical warfare: A public health integration review. *Medicine.* 2025 May 2;104(18):e42289.
40. Basiri R, Seidu B, Rudich M. Exploring the interrelationships between diabetes, nutrition, anxiety, and depression: implications for treatment and prevention strategies. *Nutrients.* 2023 Sep 30;15(19):4226.
41. Paul-Chima UO, Nneoma UC, Bulhan S. Metabolic immunobridge: Could adipose-derived extracellular vesicles be the missing link between obesity, autoimmunity, and drug-induced hepatotoxicity?. *Medical Hypotheses.* 2025 Sep 28:111776.

42. Yadav S, Hong YR, Westen S, Marlow NM, Haller MJ, Walker AF. Sociodemographic factors associated with major depressive episodes and suicidal ideation among emerging adults with diabetes in the US. *Frontiers in endocrinology*. 2023 Dec 7;14:1276336.
43. Ugwu OP, Alum EU, Ugwu JN, Eze VH, Ugwu CN, Ogenyi FC, Okon MB. Harnessing technology for infectious disease response in conflict zones: Challenges, innovations, and policy implications. *Medicine*. 2024 Jul 12;103(28):e38834.
44. Sweileh WM. Analysis of global research output on diabetes depression and suicide. *Annals of general psychiatry*. 2018 Oct 23;17(1):44.
45. Mason J, Meal A, Shaw I, Adams GG. Outcomes of mindfulness-based stress reduction and mindfulness-based cognitive therapy in adults with diabetes: a systematic review. *Diabetes Treat*. 2018;10:2574-7568.
46. Paul-Chima UO, Ugwu CN, Alum EU. Integrated approaches in nutraceutical delivery systems: optimizing ADME dynamics for enhanced therapeutic potency and clinical impact. *RPS Pharmacy and Pharmacology Reports*. 2024 Oct;3(4):rqae024.
47. Ugwu OP, Ogenyi FC, Ugwu CN, Ugwu MN. Gut microbiota-derived metabolites as early biomarkers for childhood obesity: A policy commentary from urban African populations. *Obesity Medicine*. 2025 Sep 1;57:100641.
48. Isaac Edyedu PMA, Ugwu OPC, Ugwu CN, Alum EU, et al. The role of pharmacological interventions in managing urological complications during pregnancy and childbirth: A review. *Medicine*. 2025;104(7):e41381.
49. Alum EU, Ugwu OPC, Obeagu EI, et al. Nutritional care in diabetes mellitus: A comprehensive guide. *Int J Innov Appl Res*. 2023;11(12):16-25.
50. Obeagu EI, Ahmed YA, Obeagu GU, Bunu UO, Ugwu OPC, Alum EU. Biomarkers of breast cancer: Overview. *Int J Curr Res Biol Med*. 2023;1:8-16.
51. Uti DE, Alum EU, Atangwho IJ, Ugwu OPC, et al. Lipid-based nano-carriers for the delivery of anti-obesity natural compounds: Advances in targeted delivery and precision therapeutics. *J Nanobiotechnol*. 2025;23:336.
52. Ugwu CN, Ugwu OPC, Alum EU, Eze VHU, Basajja M, Ugwu JN, Ogenyi FC, et al. Medical preparedness for bioterrorism and chemical warfare: A public health integration review. *Medicine*. 2025;104(18):e42289.
53. Obeagu EI, Scott GY, Amekpor F, Ugwu OPC, Alum EU. COVID-19 infection and diabetes: A current issue. *Int J Innov Appl Res*. 2023;11(1):25-30.
54. Offor CE, Ugwu OPC, Alum EU. Anti-diabetic effect of ethanol leaf extract of *Allium sativum* on albino rats. *Int J Pharm Med Sci*. 2014;4(1):1-3.
55. Asogwa FC, Okechukwu PCU, Esther UA, Chinedu OE, Nzubechukwu E. Hygienic and sanitary assessment of street food vendors in selected towns of Enugu North District, Nigeria. *Am-Eurasian J Sci Res*. 2015;10(1):22-26.
56. Alum EU, Uti DE, Agah VM, Orji OU, Nkeiru N, et al. Physico-chemical and bacteriological analysis of water used for drinking and domestic purposes in Amaozara Ozizza, Afikpo North, Nigeria. *Niger J Biochem Mol Biol*. 2023;38(1):1-8.
57. Ugwu OPC, Alum EU, Okon MB, Obeagu EI. Mechanisms of microbiota modulation: Implications for health, disease, and therapeutic interventions. *Medicine*. 2024;103(19):e38088.
58. Ezekwe CI, Uzomba CR, Ugwu OPC. Effect of methanol extract of *Talinum triangulare* on hematology and liver parameters in rats. *Glob J Biotechnol Biochem*. 2013;8(2):51-60.
59. Alum EU, Inya JE, Ugwu OPC, Obeagu EI, Alope C, Aja PM, Okpata MG, et al. Ethanolic leaf extract of *Datura stramonium* attenuates methotrexate-induced biochemical alterations in Wistar rats. *RPS Pharmacol Rep*. 2023;2(1):1-6.
60. Ugwu OPC, Erisa K, Inyangat R, Obeagu EI, et al. Indigenous medicinal plants for managing diabetes in Uganda: Ethnobotanical and pharmacotherapeutic insights. *INOSR Exp Sci*. 2023;12(2):214-224.
61. Alum EU, Aja W, Ugwu OPC. Vitamin composition of ethanol leaf and seed extracts of *Datura stramonium*. *Avicenna J Med Biochem*. 2023;11(1):92-97.
62. Ezenwaji CO, Alum EU, Ugwu OPC. Digital health in pandemic preparedness and response: Securing global health? *Glob Health Action*. 2024;17(1):2419694.
63. Adonu CC, Ugwu OP, Bawa A, Ossai EC, Nwaka AC. Intrinsic blood coagulation studies in patients with diabetes and hypertension. *Int J Pharm Med Bio Sci*. 2013;2(2):36-45.
64. Offor CE, Ugwu PC, Okechukwu PM, Igwenyi IO. Proximate and phytochemical analyses of *Terminalia catappa* leaves. *Eur J Appl Sci*. 2015;7(1):9-11.
65. Enechi YS, Ugwu OC, Ugwu KK, Ugwu OPC, Omeh N. Evaluation of antinutrient levels of *Ceiba pentandra* leaves. *IJRRPAS*. 2013;3(3):394-400.

66. Alum EU, Uti DE, Ugwu OPC, Alum BN, Edeh FO, Ainebyoona C. Microbiota in cancer development and treatment. *Discov Oncol.* 2025;16(1):646.
67. Asogwa FC, Okoye COB, Ugwu OPC, Edwin N, Alum EU, Egwu CO. Phytochemistry and antimicrobial assay of *Jatropha curcas* extracts. *Eur J Appl Sci.* 2015;7(1):12-16.
68. Enechi OC, Oluka HI, Ugwu PCO. Acute toxicity and ameliorative properties of *Alstonia boonei* leaf extract on diabetic rats. *Afr J Biotechnol.* 2014;13(5).
69. Alum EU, Obeagu EI, Ugwu OPC. Enhancing water, sanitation, and hygiene for diarrhoea control and SDGs: A review. *Medicine.* 2024;103(38):e39578.
70. Odo CE, Nwodo OFC, Joshua PE, Ugwu OPC, Okonkwo CC. Anti-diarrhoeal effect of chloroform-methanol extract of *Persea americana* seeds in rats. *J Pharm Res.* 2013;6(3):331-335.
71. Ugwu OPC, Obeagu EI, Alum EU, Michael M, et al. Effect of ethanol leaf extract of *Chromolaena odorata* on hepatic markers in diabetic rats. *IAA J Appl Sci.* 2023;9(1):46-56.
72. Ibiam UA, Alum EU, Orji OU, Aja PM, Nwamaka EN, Ugwu OPC, et al. Anti-inflammatory effects of *Buchholzia coriacea* leaf extract in arthritic rats. *Indo Am J Pharm Sci.* 2018;5(7):6341-6357.
73. Obeagu EI, Obeagu GU, Odo EO, Alum EU. Nutritional approaches for enhancing immune competence in HIV-positive individuals. *IDOSR J Appl Sci.* 2024;9(1):40-50.
74. Obeagu EI, Alum EU, Ugwu OPC. Hcpidin: Gatekeeper of iron in malaria resistance. *Newport Int J Res Med Sci.* 2023;4(2):1-8.
75. Nyamboga TO, Ugwu OPC, Ugwu JN, et al. Biotechnological innovations in soil health management: a systematic review of integrating microbiome engineering, bioinformatics, and sustainable practices. *Cogent Food Agric.* 2025;11(1):2519811.
76. Madu ANB, Alum EU, Aloh HE, Ugwu OPC, Obeagu EI, Uti DE, Egba SI, Ukaidi CUA. The price of progress: Assessing the financial costs of HIV/AIDS management in East Africa. *Medicine.* 2025;104(18):e42300.
77. Alum EU, Ugwu OPC. Beyond pregnancy: Understanding long-term implications of gestational diabetes mellitus. *INOSR Sci Res.* 2024;11(1):63-71.
78. Ugwu OPC, Alum EU, Okon MB, Aja PM, Obeagu EI, Onyeneke EC. Anti-nutritional and GC-MS analysis of ethanol root extract and fractions of *Sphenocentrum jollyanum*. *RPS Pharmacol Pharm Rep.* 2023;2(2):rqad007.
79. Eze VHU, Eze CE, Mbabazi A, Ugwu CN, Ugwu PO, Ogenyi CF, Ugwu JN, et al. Qualities and characteristics of a good scientific research writing: Step-by-step approaches. *IAA J Appl Sci.* 2023;9(2):71-76.
80. Igwenyi IO, Nchi PO, Okechukwu UPC, Igwenyi IP, Obasi DC, Edwin N. Nutritional potential of *Azadirachta indica* seeds. *Indo Am J Pharm Sci.* 2017;4(2):477-482.
81. Enechi OC, Oluka IH, Ugwu OPC, Omeh YS. Effect of ethanol leaf extract of *Alstonia boonei* on lipid profile of alloxan-induced diabetic rats. *Afr J Biotechnol.* 2013;24.
82. Ugwu OPC. Anti-malaria effect of ethanol extract of *Moringa oleifera* leaves on malaria-induced mice. *University of Nigeria Nsukka;* 2011:39.
83. Alum EU, Ugwu OPC, Obeagu EI. Nutritional interventions for cervical cancer patients: Beyond conventional therapies. *J Cancer Res Cell Ther.* 2024;8(1):1-6.
84. Obeagu EI, Obeagu GU. Advancements in immune augmentation strategies for HIV patients. *IAA J Biol Sci.* 2024;11(1):1-11.
85. Okechukwu PU, Nzubechukwu E, Ogbanshi ME, Ezeani N, Nworie MO. Effect of ethanol leaf extract of *Jatropha curcas* on chloroform-induced hepatotoxicity in albino rats. *Glob J Biotech Biochem.* 2015;10:11-15.
86. Ilozue NM, Ikezu UP, Okechukwu PCU. Antimicrobial and phytochemical screening of *Persea americana* seed extracts. *IOSR J Pharm Biol Sci.* 2014;9(2):23-25.
87. Onyeze R, Udeh SM, Akachi B, Ugwu OP. Isolation and characterization of fungi associated with spoilage of corn (*Zea mays*). *Int J Pharm Med Biol Sci.* 2013;2(3):86-91.
88. Obeagu EI, Alum EU, Ugwu OPC. Hcpidin: The gatekeeper of iron in malaria resistance. *Newport Int J Res Med Sci.* 2023;4:1-8.
89. Obeagu EI, Alum EU, Obeagu GU, Ugwu OPC. Prostate cancer: Review on risk factors. *Eurasian Exp J Public Health.* 2023;4(1):4-7.
90. Offor CE, Okaka ANC, Ogbugo SO, Egwu CO, Okechukwu PC. Effects of ethanol leaf extract of *Pterocarpus santalinoides* on haemoglobin, packed cell volume and platelets. *IOSR J Nurs Health Sci.* 2015;4:108-112, 93.

91. Ofor C, Aja PC, Ugwu O, Agbafor KN. Effects of ethanol leaf extract of *Gmelina arborea* on serum proteins in albino rats. *Glob J Environ Res.* 2015;9(1):1-4.
92. Alum EU, Uti DE, Obeagu EI, Ugwu OPC, Alum BN. Cancer's psychosocial aspects: Impact on patient outcomes. *Elite J Med.* 2024;2(6):32-42.
93. Alum EU, Ugwu OPC, Egba SI, Uti DE, Alum BN. Climate variability and malaria transmission: Unravelling the complex relationship. *INOSR Sci Res.* 2024;11(2):16-22.
94. Alum EU, Obeagu EI, Ugwu OPC, Egba SI, EjimUti DE, Ukaidi CUA, et al. Confronting dual challenges: Substance abuse and HIV/AIDS. *Elite J HIV.* 2024;2(5):1-8.

CITE AS: Kungu Erisa (2026). Combined Chemical Exposures and Synergistic Toxicity: Unraveling Biochemical Interactions in the Anthropocene. IAA Journal of Applied Sciences 14(1):90-97. <https://doi.org/10.59298/IAAJAS/2026/1419097>