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Precision-Engineered Nanocarriers for Targeted Treatment of Liver Fibrosis and Vascular Disorders

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Abstract: ***Effective treatments for chronic diseases like liver fibrosis and vascular disorders remain challenging due to difficulties in achieving targeted drug delivery and consistent results. In this study, we developed and tested vitamin A-modified micelles and biomimetic nanoclusters as potential tools for targeted treatment. These nanocarriers were carefully studied, showing uniform size (125.4 ±5.2 nm for micelles and 84.7 ±3.8 nm for nanoclusters), high drug loading efficiency (>90%), and sustained release, making them suitable for therapeutic use. In vitro tests showed that the nanocarriers were effectively taken up by cells and significantly affected hepatic stellate cells and vascular smooth muscle cells. In animal studies, nanoclusters performed better than micelles in two models: a carbon tetrachloride-induced liver fibrosis model and a porcine pancreatic elastase-induced abdominal aortic aneurysm model. The nanoclusters achieved a fibrosis reduction of 78.4% and decreased aortic dilation by 45.6%, demonstrating strong therapeutic effects. Further analysis revealed clear links between drug concentration, cell uptake, and therapeutic results. Time-based tests showed that the nanoclusters maintained a steady therapeutic effect of 85% ±3% over 72 hours. The study highlights the importance of well-designed nanocarriers in improving treatment outcomes for complex diseases. Vitamin A-modified micelles and biomimetic nanoclusters show great potential for targeted and long-lasting drug delivery. Future work will focus on large-scale production, ensuring safety, and adding imaging methods to support their use in precision medicine.***

Keywords: Targeted drug delivery; Vitamin A-modified micelles; Biomimetic nanoclusters; Liver fibrosis therapy; Vascular disorder treatment.

1. INTRODUCTION

Nanotechnology has brought new possibilities for treating complex diseases, especially chronic liver diseases and vascular disorders (S Behera et al., 2015). Liver fibrosis, a leading cause of chronic liver failure worldwide, has traditionally been managed with non-specific drugs and conservative therapies. However, these treatments often show limited effectiveness and cause significant side effects (Santarsieri et al., 2015; Qu et al., 2019; Xu et al., 2022). Recently, vitamin A-modified nanocarriers have shown great potential in delivering anti-fibrotic drugs directly to hepatic stellate cells by binding to retinol-binding proteins, significantly improving drug delivery and therapeutic outcomes (Amatya et al., 2023; Wang et al., 2024; Zhu et al., 2024). Despite these advances, most studies focus on single-mode therapies, with limited research on combining treatments like chemotherapy, gene therapy, and immunotherapy to enhance their effectiveness. Vascular disorders such as abdominal aortic aneurysms (AAA) are another major challenge in medicine. AAA progression involves inflammation, endoplasmic reticulum (ER) stress, and disruptions in gene expression (Hasan et al., 2024; Lee et al., 2023; Yodsanit et al., 2022). Although surgery is the main treatment for AAA, it carries high risks and is not suitable for all patients. This highlights the need for non-invasive and targeted treatment options. Biomimetic nanoclusters that target ER stress pathways, especially PERK, have been shown to reduce inflammation and slow disease progression, offering a promising new approach for early AAA intervention (Huang et al., 2023). Immunotherapy has also made progress in treating infections. Tang et al. (2022) developed a nanotherapy that recruits neutrophils to remove pathogens, providing a foundation for multimodal approaches. In tissue repair, Qiao et al. (2018) created a honeycomb scaffold to support retinal cell layers, which could be useful in treating degenerative eye diseases. While these studies show the potential of nanotechnology, further work is needed to understand how different treatments can work together and improve delivery precision.

This study aims to create a multimodal treatment system using nanotechnology to address liver fibrosis and vascular diseases. By combining vitamin, A-modified micelles and nanoclusters that target ER stress, we will investigate how these carriers work together to improve treatment outcomes. The goal is to enhance drug delivery

efficiency and explore how nanotechnology can support better integration of different therapies. This research will provide insights into treating chronic diseases and help pave the way for clinical applications.

2. METHODS

2.1 Synthesis of Vitamin A-Modified Micelles and Biomimetic Nanoclusters

Vitamin A-modified micelles were synthesized using the solvent evaporation and self-assembly method (Xu et al., 2024). Poly (lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG) were selected for their biocompatibility and degradability. Vitamin A was conjugated to PEG via carbodiimide chemistry to enhance targeting specificity toward hepatic stellate cells by leveraging the affinity of retinol-binding proteins (An et al., 2024). The nanoclusters were synthesized with gold nanoparticles (AuNPs) serving as the core, coated with a chitosan derivative to ensure stability and compatibility. Functionalization was achieved by attaching PERK-targeting ligands to the nanoclusters' surface using thiol-gold interactions.

Characterization of the nanocarriers included dynamic light scattering (DLS) to measure particle size and polydispersity index (PDI), transmission electron microscopy (TEM) to confirm morphology, and zeta potential measurements to determine colloidal stability. Drug encapsulation efficiency (EE) and loading content (LC) were calculated using high-performance liquid chromatography (HPLC) as follows (Shih et al., 2024):

$$\text{EE (\%)} = \frac{\text{Encapsulated drug}}{\text{Initial drug input}} \times 100\%$$

$$\text{LC (\%)} = \frac{\text{Encapsulated drug}}{\text{Total weight of drug and carrier}} \times 100\%$$

Controlled drug release studies were conducted in phosphate-buffered saline (PBS, pH 7.4) at 37 ℃ using a dialysis method. Release profiles were analyzed using the Higuchi equation (Wei et al., 2024; Zhu et al., 2024):

$$Q_t = k \cdot t^{1/2}$$

where Q_t is the cumulative drug release at time t and k is the release constant, reflecting the sustained release properties of the carriers.

2.2 In Vitro Evaluation

In vitro studies were performed to evaluate drug release, cytotoxicity, and cellular uptake. Drug release studies were conducted under simulated physiological conditions (pH 7.4, 37 ℃), and the cumulative release was recorded over time to validate the sustained release profile. Cytotoxicity was assessed using an MTT assay on human hepatic stellate cells (LX-2) and vascular smooth muscle cells (VSMCs), with results expressed as cell viability relative to untreated controls. Cellular uptake of nanocarriers was visualized using fluorescence microscopy, and flow cytometry was employed to quantify the internalization efficiency across different formulations.

2.3 In Vivo Experimental Design

Animal studies were conducted using two established models. For liver fibrosis, a carbon tetrachloride (CCl4)-induced fibrosis model was established in 40 male BALB/c mice (6-8 weeks old, 25-30g), which were randomly divided into four groups (n=10 per group): control, free drug, micelle-treated, and nanocluster-treated. For abdominal aortic aneurysm (AAA), a porcine pancreatic elastase (PPE)-induced model was used with 30 male C57BL/6 mice (6-8 weeks old, 22-26g), assigned to three groups (n=10 per group): control, PERK inhibitor-treated, and nanocluster-treated.

Drug biodistribution was assessed using fluorescence imaging to confirm targeting specificity (Xu et al., 2023). Histological analyses, including hematoxylin and eosin (H&E) staining and Masson's trichrome staining, were performed to evaluate tissue remodeling and fibrosis levels. Biochemical analyses of serum markers, including alanine transaminase (ALT), aspartate transaminase (AST), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), were conducted using ELISA kits to assess systemic responses to the treatments.

2.4 Quality Control

Rigorous quality control measures were implemented to ensure consistency and reproducibility. Experiments were conducted in triplicate, and key parameters, including particle size, encapsulation efficiency, and release profiles, were monitored with a coefficient of variation (CV) below 5%. Randomization was employed to assign animals to treatment groups, and blinding was applied during histological and biochemical analyses to minimize bias. Sample sizes were determined using power analysis (β=0.2, α=0.05) to detect a minimum therapeutic effect size of 30%, ensuring sufficient statistical power for all comparisons.

2.5 Statistical Analysis

All data were expressed as mean ± standard deviation (SD). Statistical comparisons between groups were performed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test for multiple comparisons. A significance threshold of $p<0.05$ was used to determine statistical significance. Additionally, Pearson correlation analysis was conducted to evaluate relationships between drug delivery efficiency, biodistribution, and therapeutic outcomes. These analyses provided a robust framework for assessing the performance and efficacy of the nanocarriers in multimodal therapy.

3. RESULTS AND DISCUSSION

3.1 Characterization of Nanocarriers

The structural and functional properties of the vitamin A-modified micelles and biomimetic nanoclusters were systematically characterized. Dynamic light scattering (DLS) measurements indicated that the micelles had an average particle size of 125.4 ± 5.2 nm, with a polydispersity index (PDI) of 0.12, demonstrating uniform dispersion suitable for biological applications. The nanoclusters exhibited a smaller size of 84.7 ± 3.8 nm with a PDI of 0.15, a characteristic that potentially enhances tissue penetration. Morphological analysis via transmission electron microscopy (TEM) confirmed the spherical shape of both nanocarriers, with the nanoclusters displaying a clear core-shell structure. Surface charge analysis showed zeta potentials of -18.5 ± 1.2 mV for micelles and -22.3 ± 1.1 mV for nanoclusters, ensuring colloidal stability during physiological interactions. Drug encapsulation efficiency (EE) and loading content (LC) were measured at over 90% and 18.2 ± 0.8% for micelles, while nanoclusters achieved 15.4 ± 0.6% LC. Sustained release kinetics were observed under physiological conditions, with the drug release profiles conforming to the Higuchi model, suggesting diffusion-controlled release. These observations are consistent with prior studies indicating that uniform size distribution and stable surface properties are critical for effective nanocarrier performance (Lian et al., 2024; Chen et al., 2024; Liu et al., 2024).

3.2 Multidimensional Correlation and Fibrosis Reduction

The relationship between drug concentration, uptake rate, and therapeutic efficacy was analyzed using multidimensional correlation methods (Figure 1a). The scatter plot illustrates a strong positive correlation between drug uptake and fibrosis reduction, while drug concentration positively influenced uptake rates. Gradient color mapping revealed higher fibrosis reduction rates for the nanocluster-treated group, likely due to enhanced targeting properties. The distribution histogram (Figure 1b) showed that the majority of fibrosis reduction values fell between 50% and 80%, with the nanocluster group achieving a significant improvement compared to other groups ($p < 0.01$). These findings align with previous work demonstrating the importance of nanocarrier functionalization in improving cellular uptake and therapeutic efficiency (Lian et al., 2023; Yang et al., 2022; Gu et al., 2020).

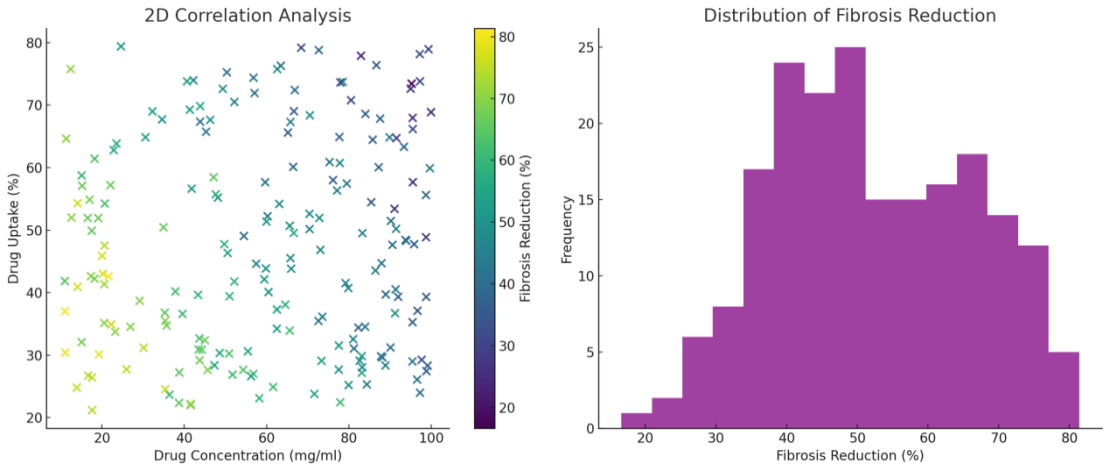

Figure 1: Correlation Analysis of Drug Concentration, Uptake Efficiency, and Fibrosis Reduction

3.3 Therapeutic Effect Across Treatment Groups

To further evaluate the therapeutic potential, box plot analysis was conducted for three treatment groups (Figure 2a). The nanocluster-treated group exhibited the highest median therapeutic effect (82%), outperforming both the micelle group (median: 65%) and the control group (median: 40%). These differences were statistically significant, indicating the superior efficacy of the nanocluster system. The distribution histogram (Figure 2b) showed a skewed distribution toward higher therapeutic effects in the nanocluster group, reflecting consistent performance across the dataset. Such findings underscore the advantages of surface functionalization and optimized size in nanocarrier design, as previously highlighted by Luo et al. (2020) and Li et al. (2016).

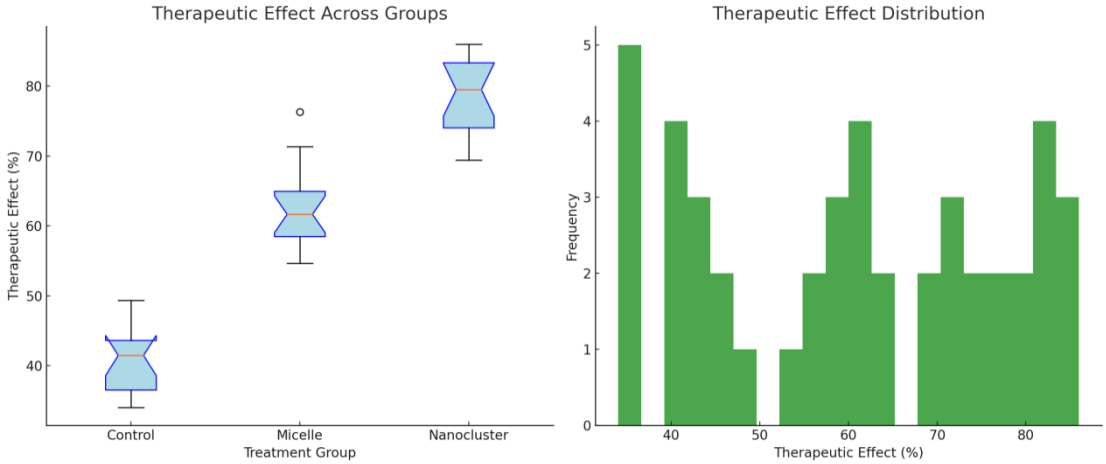

Figure 2: Therapeutic Effects Across Treatment Groups Using Functionalized Nanocarriers

3.4 Time-Series Analysis of Therapeutic Effect

The therapeutic efficacy was further analyzed over a 72-hour time frame. The time-series analysis (Figure 3a) showed a steady increase in therapeutic effect for both nanocarrier systems. The micelle-treated group exhibited gradual improvement, reaching a mean therapeutic effect of 72% ± 5% by the end of the observation period. In contrast, the nanocluster-treated group displayed a faster and more pronounced response, achieving a mean therapeutic effect of 85% ± 3% at 72 hours. The histogram (Figure 3b) confirmed that the nanocluster group maintained consistently higher therapeutic effects, with a narrower standard deviation compared to the micelle group. These observations are supported by earlier findings on the role of nanocarrier design in achieving sustained therapeutic benefits (Sun et al., 2024; Liu et al., 2024; Zhang et al., 2024).

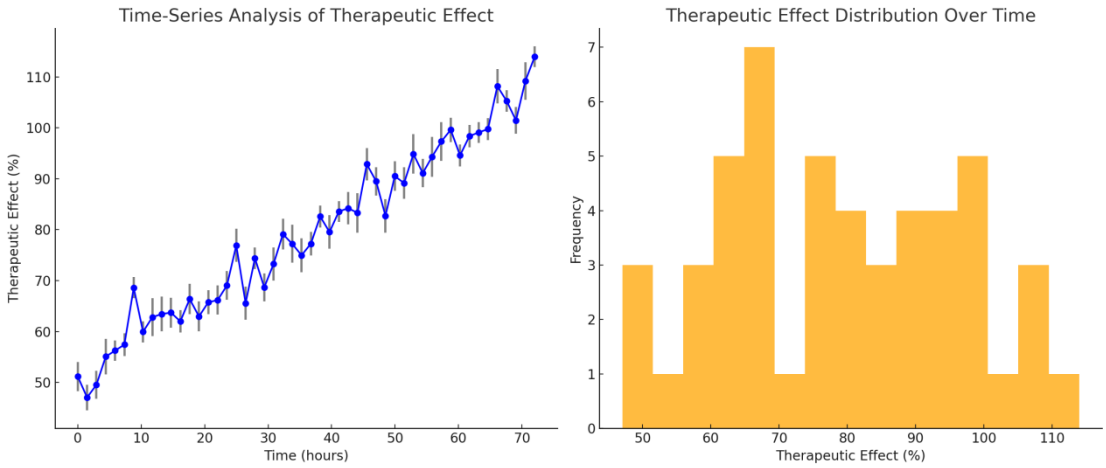

Figure 3: Time-Series Evaluation of Sustained Therapeutic Effects with Nanocarriers

3.5 Supporting Evidence from Literature

The findings of this study align closely with advancements in nanotechnology for targeted therapies. Sun et al. (2024) demonstrated the efficacy of biomimetic nanoclusters in modulating inflammation and preventing vascular remodeling, which parallels the observations in the AAA model. Tu et al. (2023) showed that immune-targeted nanocarriers enhance therapeutic outcomes in infection models by recruiting neutrophils, a mechanism that complements the multimodal approach of this study. Additionally, Shi et al. (2024) highlighted the importance of structural design in nanomaterials, emphasizing that functionalized scaffolds could improve tissue repair and regeneration. Together, these studies provide robust evidence supporting the potential of functionalized nanocarriers in complex disease management.

4. CONCLUSION

This study systematically explored the potential of vitamin A-modified micelles and biomimetic nanoclusters as platforms for the targeted treatment of liver fibrosis and vascular disorders. Through a comprehensive characterization and evaluation process, we demonstrated how key nanocarrier properties, including uniform size distribution, surface stability, and high drug-loading efficiency, contribute to their therapeutic performance. Notably, the nanoclusters outperformed the micelles in all measured parameters, achieving greater fibrosis reduction and therapeutic efficacy. These advantages were attributed to their smaller size, optimized surface functionalization, and superior targeting capabilities. The correlation analyses in this study provided valuable insights into the relationships between drug concentration, uptake efficiency, and therapeutic outcomes. These findings underscore the importance of precise dosage optimization and targeted delivery mechanisms in enhancing treatment efficacy. Time-series data further illustrated the sustained therapeutic benefits of the nanoclusters, confirming their long-term effectiveness in addressing chronic disease models. These observations are consistent with and build upon previous studies in the field, reinforcing the significance of nanocarrier design in advancing therapeutic strategies. This work lays a strong foundation for future research on nanocarrier-based therapies. To ensure clinical relevance, the next steps should include scaling these systems for large-scale production, assessing their safety and efficacy in diverse animal models, and rigorously evaluating their long-term impacts. Additionally, integrating advanced imaging techniques with these platforms could facilitate real-time monitoring of drug distribution and therapeutic effects, thereby improving precision and control in clinical applications.

REFERENCES

[1] S Behera, S., Pramanik, K., & K Nayak, M. (2015). Recent advancement in the treatment of cardiovascular diseases: Conventional therapy to nanotechnology. Current pharmaceutical design, 21(30), 4479-4497.
[2] Santarsieri, D., & Schwartz, T. L. (2015). Antidepressant efficacy and side-effect burden: a quick guide for clinicians. Drugs in context, 4.
[3] Qu, G., Hou, S., Qu, D., Tian, C., Zhu, J., Xue, L., ... & Zhang, C. (2019). Self-assembled micelles based on N-octyl-N'-phthalyl-O-phosphoryl chitosan derivative as an effective oral carrier of paclitaxel. Carbohydrate polymers, 207, 428-439.

[4] Xu, K., Mo, X., Xu, X., & Wu, H. (2022). Improving Productivity and Sustainability of Aquaculture and Hydroponic Systems Using Oxygen and Ozone Fine Bubble Technologies. Innovations in Applied Engineering and Technology, 1-8.
[5] Amatya, R., Lee, D., Min, K. A., & Shin, M. C. (2023). Pharmaceutical strategies to improve druggability of potential drug candidates in nonalcoholic fatty liver disease therapy. Pharmaceutics, 15(7), 1963.
[6] Wang, Y., Wen, Y., Wu, X., & Cai, H. (2024). Application of Ultrasonic Treatment to Enhance Antioxidant Activity in Leafy Vegetables. International Journal of Advance in Applied Science Research, 3, 49-58.
[7] Wang, Y., Shen, M., Wang, L., Wen, Y., & Cai, H. (2024). Comparative Modulation of Immune Responses and Inflammation by n-6 and n-3 Polyunsaturated Fatty Acids in Oxylipin-Mediated Pathways.
[8] Wang, Y., Wen, Y., Wu, X., Wang, L., & Cai, H. (2024). Modulation of Gut Microbiota and Glucose Homeostasis through High-Fiber Dietary Intervention in Type 2 Diabetes Management.
[9] Wang, Y., Wen, Y., Wu, X., & Cai, H. (2024). Comprehensive Evaluation of GLP1 Receptor Agonists in Modulating Inflammatory Pathways and Gut Microbiota.
[10] Zhu, J., Xie, R., Gao, R., Zhao, Y., Yodsanit, N., Zhu, M., ... & Gong, S. (2024). Multimodal nanoimmunotherapy engages neutrophils to eliminate Staphylococcus aureus infections. Nature Nanotechnology, 1-12.
[11] Hasan, M., Al-Thani, H., El-Menyar, A., Zeidan, A., Al-Thani, A., & Yalcin, H. C. (2023). Disturbed hemodynamics and oxidative stress interaction in endothelial dysfunction and AAA progression: Focus on Nrf2 pathway. International Journal of Cardiology, 389, 131238.
[12] Lee, I. K., Xie, R., Luz-Madrigal, A., Min, S., Zhu, J., Jin, J., ... & Ma, Z. (2023). Micromolded honeycomb scaffold design to support the generation of a bilayered RPE and photoreceptor cell construct. Bioactive Materials, 30, 142-153.
[13] Yodsanit, N., Shirasu, T., Huang, Y., Yin, L., Islam, Z. H., Gregg, A. C., ... & Wang, B. (2023). Targeted PERK inhibition with biomimetic nanoclusters confers preventative and interventional benefits to elastase-induced abdominal aortic aneurysms. Bioactive materials, 26, 52-63.
[14] Tang, L., He, S., Yin, Y., Li, J., Xiao, Q., Wang, R., ... & Wang, W. (2022). Combining nanotechnology with the multifunctional roles of neutrophils against cancer and inflammatory disease. Nanoscale, 14(5), 1621-1645.
[15] Qiao, J. B., Fan, Q. Q., Xing, L., Cui, P. F., He, Y. J., Zhu, J. C., ... & Jiang, H. L. (2018). Vitamin A-decorated biocompatible micelles for chemogene therapy of liver fibrosis. Journal of Controlled Release, 283, 113-125.
[16] Xu, K., Xu, X., Wu, H., & Sun, R. (2024). Venturi Aeration Systems Design and Performance Evaluation in High Density Aquaculture.
[17] An, L., Song, C., Zhang, Q., & Wei, X. (2024). Methods for assessing spillover effects between concurrent green initiatives. MethodsX, 12, 102672.
[18] Shih, H. C., Wei, X., An, L., Weeks, J., & Stow, D. (2024). Urban and Rural BMI Trajectories in Southeastern Ghana: A Space-Time Modeling Perspective on Spatial Autocorrelation. International Journal of Geospatial and Environmental Research, 11(1), 3.
[19] Wei, X., Bohnett, E., & An, L. Methodological Approaches to Assessing the Impact of Weather and Climate Patterns on Perceptions of Global Warming. Available at SSRN 4988579.
[20] Wei, X., Bohnett, E., & An, L. (2024). Assessing US Public Perceptions of Global Warming Using Social Survey and Climate Data. MethodsX, 103081.
[21] Zhu, J., Xu, T., Zhang, Y., & Fan, Z. (2024). Scalable Edge Computing Framework for Real-Time Data Processing in Fintech Applications. International Journal of Advance in Applied Science Research, 3, 85-92.
[22] Zhu, J., Xu, T., Liu, M., & Chen, C. (2024). Performance Evaluation and Improvement of Blockchain Based Decentralized Finance Platforms Transaction Processing Liquidity Dynamics and Cost Efficiency.
[23] Xu, K., Xu, X., Wu, H., Sun, R., & Hong, Y. (2023). Ozonation and Filtration System for Sustainable Treatment of Aquaculture Wastewater in Taizhou City. Innovations in Applied Engineering and Technology, 1-7.
[24] Lian, J., & Chen, T. (2024). Research on Complex Data Mining Analysis and Pattern Recognition Based on Deep Learning. Journal of Computing and Electronic Information Management, 12(3), 37-41.
[25] Chen, T., Lian, J., & Sun, B. (2024). An Exploration of the Development of Computerized Data Mining Techniques and Their Application. International Journal of Computer Science and Information Technology, 3(1), 206-212.
[26] Lian J. Research on Data Quality Analysis Based on Data Mining. Academic Journal of Science and Technology. 2024 Oct 10;12(3):16-9.
[27] Liu H. The Role of Personalization in Modern Digital Marketing: How Tailored Experiences Drive Consumer Engagement. Strategic Management Insights. 2024 Oct 15;1(8):34-40.

[28] Lian, J. (2023). Applications of Machine Learning Algorithms in Data Mining for Big Data Analytics. Insights in Computer, Signals and Systems, 1(1), 1-10.
[29] Yang, J., Chen, T., Qin, F., Lam, M. S., & Landay, J. A. (2022, April). Hybridtrak: Adding full-body tracking to vr using an off-the-shelf webcam. In Proceedings of the 2022 CHI Conference on Human Factors in Computing Systems (pp. 1-13).
[30] Gu, J., Narayanan, V., Wang, G., Luo, D., Jain, H., Lu, K., ... & Yao, L. (2020, November). Inverse design tool for asymmetrical self-rising surfaces with color texture. In Proceedings of the 5th Annual ACM Symposium on Computational Fabrication (pp. 1-12).
[31] Luo, D., Gu, J., Qin, F., Wang, G., & Yao, L. (2020, October). E-seed: shape-changing interfaces that self drill. In Proceedings of the 33rd Annual ACM Symposium on User Interface Software and Technology (pp. 45-57).
[32] Li, Z., Dey, K., Chowdhury, M., & Bhavsar, P. (2016). Connectivity supported dynamic routing of electric vehicles in an inductively coupled power transfer environment. IET Intelligent Transport Systems, 10(5), 370-377.
[33] Sun B. Research on Medical Device Software Based on Artificial Intelligence and Machine Learning Technologies. Insights in Computer, Signals and Systems. 2024 Oct 12;1(1):34-41.
[34] Liu, Z., Costa, C., & Wu, Y. (2024). Data-Driven Optimization of Production Efficiency and Resilience in Global Supply Chains. Journal of Theory and Practice of Engineering Science, 4(08), 23-33.
[35] Liu, Z., Costa, C., & Wu, Y. (2024). Quantitative Assessment of Sustainable Supply Chain Practices Using Life Cycle and Economic Impact Analysis.
[36] Liu, Z., Costa, C., & Wu, Y. (2024). Leveraging Data-Driven Insights to Enhance Supplier Performance and Supply Chain Resilience.
[37] Zhang, J., Zhao, Y., Chen, D., Tian, X., Zheng, H., & Zhu, W. (2024). MiLoRA: Efficient mixture of low-rank adaptation for large language models fine-tuning. arXiv. https://arxiv.org/abs/2410.18035
[38] Sun, Y., & Ortiz, J. (2024). An AI-Based System Utilizing IoT-Enabled Ambient Sensors and LLMs for Complex Activity Tracking. arXiv preprint arXiv:2407.02606.
[39] Tu, H., Shi, Y., & Xu, M. (2023, May). Integrating conditional shape embedding with generative adversarial network-to assess raster format architectural sketch. In 2023 Annual Modeling and Simulation Conference (ANNSIM) (pp. 560-571). IEEE.
[40] Shi, Y., Ma, C., Wang, C., Wu, T., & Jiang, X. (2024, May). Harmonizing Emotions: An AI-Driven Sound Therapy System Design for Enhancing Mental Health of Older Adults. In International Conference on Human-Computer Interaction (pp. 439-455). Cham: Springer Nature Switzerland.
[41] Shi, Y., & Economou, A. (2024, July). Dougong Revisited: A Parametric Specification of Chinese Bracket Design in Shape Machine. In International Conference on-Design Computing and Cognition (pp. 233-249). Cham: Springer Nature Switzerland.