**B) In order of importance, list of ten best papers of the candidate, highlighting the important discoveries/contributions described in them briefly (not to exceed 3000 words)**

**1.** Godugu, C., Patel, A.R., Doddapaneni, R., Marepally, S., Jackson, T. and Singh, M., 2013. Inhalation delivery of Telmisartan enhances intratumoral distribution of nanoparticles in lung cancer models. *Journal of controlled release*, *172*(1), pp.86-95.

**2.** Pooladanda, V., Thatikonda, S., Bale, S., Pattnaik, B., Sigalapalli, D.K., Bathini, N.B., Singh, S.B. and Godugu, C., 2019. Nimbolide protects against endotoxin-induced acute respiratory distress syndrome by inhibiting TNF-α mediated NF-κB and HDAC-3 nuclear translocation. *Cell death & disease*, *10*(2), p.81.

**3.** Thatikonda, S., Pooladanda, V., Sigalapalli, D.K. and Godugu, C., 2020. Piperlongumine regulates epigenetic modulation and alleviates psoriasis-like skin inflammation by inhibiting hyperproliferation and inflammation. *Cell death & disease*, *11*(1), p.21.

**4.** Bansod, S., Saifi, M.A., Khurana, A. and Godugu, C., 2020. Nimbolide abrogates cerulein-induced chronic pancreatitis by modulating β-catenin/Smad in a sirtuin-dependent way. *Pharmacological Research*, *156*, p.104756.

**5.** Godugu, C. and Singh, M., 2016. AlgiMatrix™-based 3D cell culture system as an in vitro tumor model: An important tool in cancer research. *Cancer Chemoprevention: Methods and Protocols*, pp.117-128.

**6.** Tekula, S., Khurana, A., Anchi, P. and Godugu, C., 2018. Withaferin-A attenuates multiple low doses of Streptozotocin (MLD-STZ) induced type 1 diabetes. *Biomedicine & Pharmacotherapy*, *106*, pp.1428-1440.

**7.** Gangadevi, V., Thatikonda, S., Pooladanda, V., Devabattula, G. and Godugu, C., 2021. Selenium nanoparticles produce a beneficial effect in psoriasis by reducing epidermal hyperproliferation and inflammation. *Journal of Nanobiotechnology*, *19*, pp.1-19.

**8.** Godugu, C., Patel, A.R., Doddapaneni, R., Somagoni, J. and Singh, M., 2014. Approaches to improve the oral bioavailability and effects of novel anticancer drugs berberine and betulinic acid. *PloS one*, *9*(3), p.e89919.

**9.** Khurana, A., Tekula, S. and Godugu, C., 2018. Nanoceria suppresses multiple low doses of streptozotocin-induced Type 1 diabetes by inhibition of Nrf2/NF-κB pathway and reduction of apoptosis. *Nanomedicine*, *13*(15), pp.1905-1922.

**10.** Pooladanda, V., Thatikonda, S., Sunnapu, O., Tiwary, S., Vemula, P.K., Talluri, M.K. and Godugu, C., 2021. iRGD conjugated nimbolide liposomes protect against endotoxin induced acute respiratory distress syndrome. *Nanomedicine: Nanotechnology, Biology and Medicine*, *33*, p.102351.

30/05/2024

**1 Inhalation Delivery of Telmisartan Enhances Intratumoral Distribution of Nanoparticles in Lung Cancer Models.*Journal of controlled release, 2013* (I.F: 11.46; Citations: 81)**

The study explores the potential of Telmisartan (Tel) and Losartan (Los), both angiotensin receptor blockers (ARBs), to enhance nanoparticle distribution and improve cancer therapy, particularly in lung cancer. The research demonstrates that inhalation of these drugs significantly increases intratumoral nanoparticle distribution, with Tel and Los showing a 5.33-fold and 14.33-fold increase, respectively, compared to controls. Notably, Tel was 2.7 times more effective than Los in this regard. A key finding of the study is the anti-fibrotic effect of Tel and Los, which helps reduce the dense collagen network in tumors—a barrier that typically hinders effective drug delivery, as shown in figure 1. Tel was especially potent, reducing Collagen 1 expression by 2.23 times compared to the untreated control and 1.70 times compared to Los. Both drugs also significantly decreased TGF-β1 levels, further indicating a reduction in tumor fibrosis. Telmisartan's dual role as an AT1 receptor blocker and PPAR-γ agonist was found to be crucial in its superior anticancer activity, particularly when administered via inhalation. The study highlights that at a four-times lower dose, Tel was nearly twice as effective as Los in reducing tumor size in both A549 orthotopic and metastatic lung cancer models. This dual pharmacophoric nature of Tel positions it as a promising candidate for combination therapy in cancer treatment. The reduction in tumor fibrosis observed with both Tel and Los treatments is significant because it suggests a modified tumor microenvironment that could enhance the delivery and effectiveness of anticancer drugs. The study ultimately suggests that ARBs, particularly Telmisartan, could play a crucial role in improving the efficacy of nanotherapeutics in cancer therapy by enhancing drug distribution and reducing fibrosis.

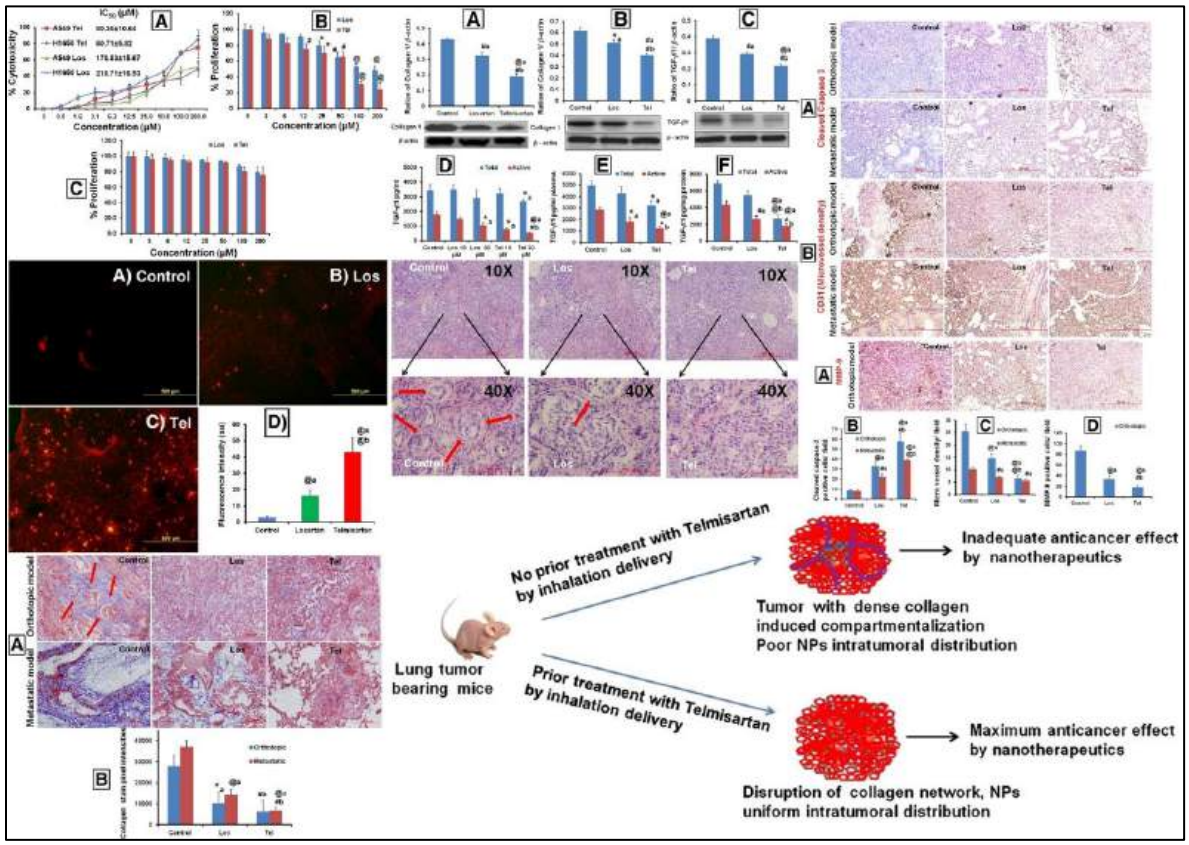


***Figure 1.***Enhanced Nanoparticle Distribution and Improved Cancer Therapy with Telmisartan and Losartan.

30/05/2024

**2 Nimbolide protects against endotoxin-induced acute respiratory distress syndrome by inhibiting TNF-α mediated NF-κB and HDAC-3 nuclear translocation.*Cell death & disease, 2019***
**(I.F: 8.1; Citations: 120)**

The study significantly advances the understanding of Acute Respiratory Distress Syndrome (ARDS) and highlights the therapeutic potential of nimbolide, a compound derived from Azadirachta indica. The research demonstrates that nimbolide effectively suppresses the production of inflammatory cytokines and chemokines, which play a pivotal role in ARDS, as shown in Figure 2. Specifically, nimbolide treatment significantly reduced TNF-α levels in lung tissues and cell culture supernatants, indicating its potential to mitigate ARDS's inflammatory component. Nimbolide also inhibits the nuclear translocation of NF-κB and HDAC-3, crucial transcription factors in regulating inflammation. The study's Western blot and immunohistochemistry analyses revealed a notable decrease in the nuclear expression of these factors in nimbolide-treated groups. Additionally, the study emphasizes nimbolide's role in epigenetic regulation by showing its inhibitory effects on histone deacetylases (HDACs). Nimbolide led to a significant, dose-dependent reduction in the expression of HDAC-1, 2, 3, and 4 in both in vitro and in vivo settings, suggesting its ability to modulate gene expression linked to inflammation. Furthermore, nimbolide demonstrated strong antioxidant properties by enhancing the expression of antioxidant proteins such as GSH, Nrf-2, SOD-1, and HO-1, essential in combating oxidative stress. Nimbolide treatment increased the levels of these proteins, thereby reducing reactive oxygen species (ROS) and maintaining redox balance. In vivo experiments confirmed nimbolide's protective effects against lipopolysaccharide (LPS)-induced ARDS in mice. Nimbolide-treated mice exhibited a reduced lung weight index, normalized body temperature, and improved physiological parameters compared to the LPS-only group. Finally, molecular docking studies supported nimbolide's therapeutic potential by showing strong interactions with TNF-α, suggesting a direct inhibitory effect on this critical inflammatory cytokine.

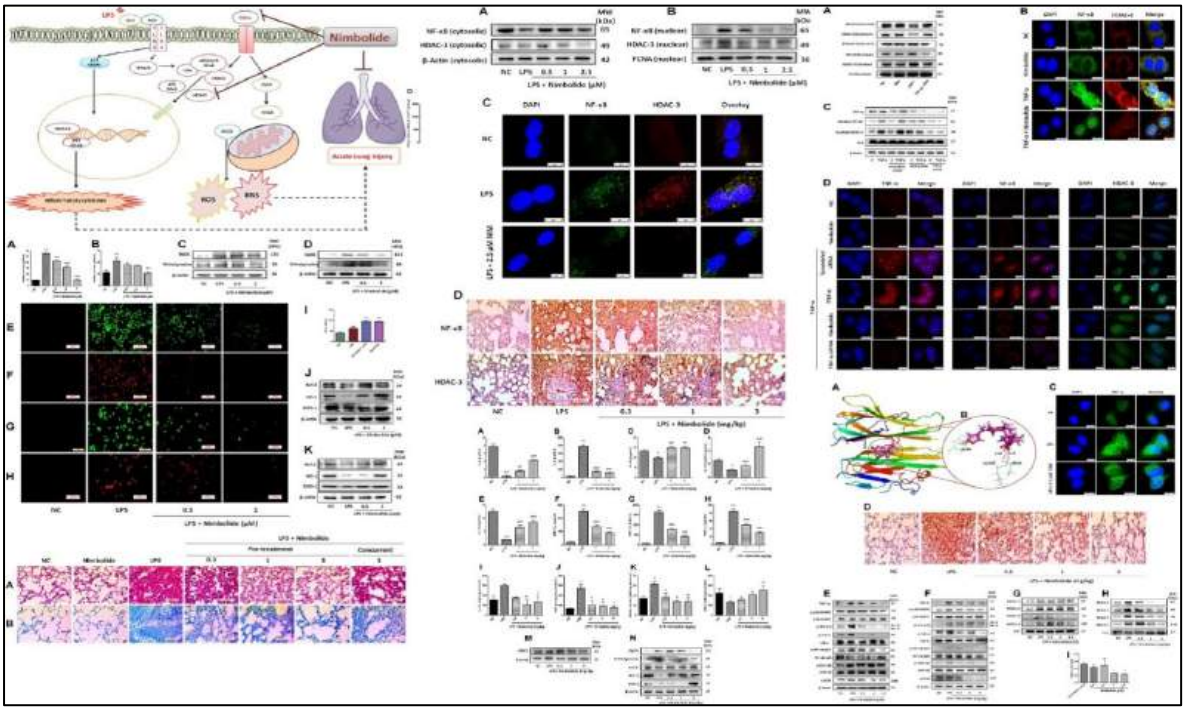


***Figure 2.***Nimbolide Protects Against Endotoxin-Induced Acute Respiratory Distress Syndrome by Inhibiting TNF-α Mediated NF-κB and HDAC-3 Nuclear Translocation.

30/05/2024

**3 Piperlongumine regulates epigenetic modulation and alleviates psoriasis-like skin inflammation via inhibition of hyperproliferation and inflammation. *Cell death & disease*, 2020 (I.F: 8.1; Citations: 96)**

The study investigates the therapeutic potential of Piperlongumine (PL) in treating psoriasis, a chronic inflammatory skin disorder. Piperlongumine was found to significantly alleviate psoriasis-like symptoms in a mouse model by exerting both anti-inflammatory and antiproliferative effects, as shown in Figure 3. The treatment led to a 40% reduction in ear thickness and a 50% decrease in epidermal hyperplasia, primarily through inhibiting the NF-κB signaling pathway. This inhibition substantially decreased the expression of key pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, by approximately 45%. Moreover, the study highlights Piperlongumine's role in epigenetic modulation, contributing to its anti-inflammatory effects. Specifically, PL was shown to decrease the acetylation of histone H3 at lysine 27 (H3K27ac) by 60% and increase the methylation of histone H3 at lysine 9 (H3K9me2) by 35%. These epigenetic modifications led to the suppression of inflammatory gene expression and decreased keratinocyte proliferation. In vivo experiments further supported PL's efficacy, as topical application in a mouse model of psoriasis resulted in a 50-60% reduction in erythema, scaling, and skin thickening compared to untreated controls. In vitro studies reinforced these findings, with PL-treated keratinocytes exhibiting a 55% reduction in proliferation rates. The study suggests that Piperlongumine's dual mechanism of action, targeting both inflammation and epigenetic pathways, presents a promising therapeutic strategy for managing psoriasis. Given these encouraging results, the study recommends further clinical investigations to evaluate PL's potential efficacy in human subjects.

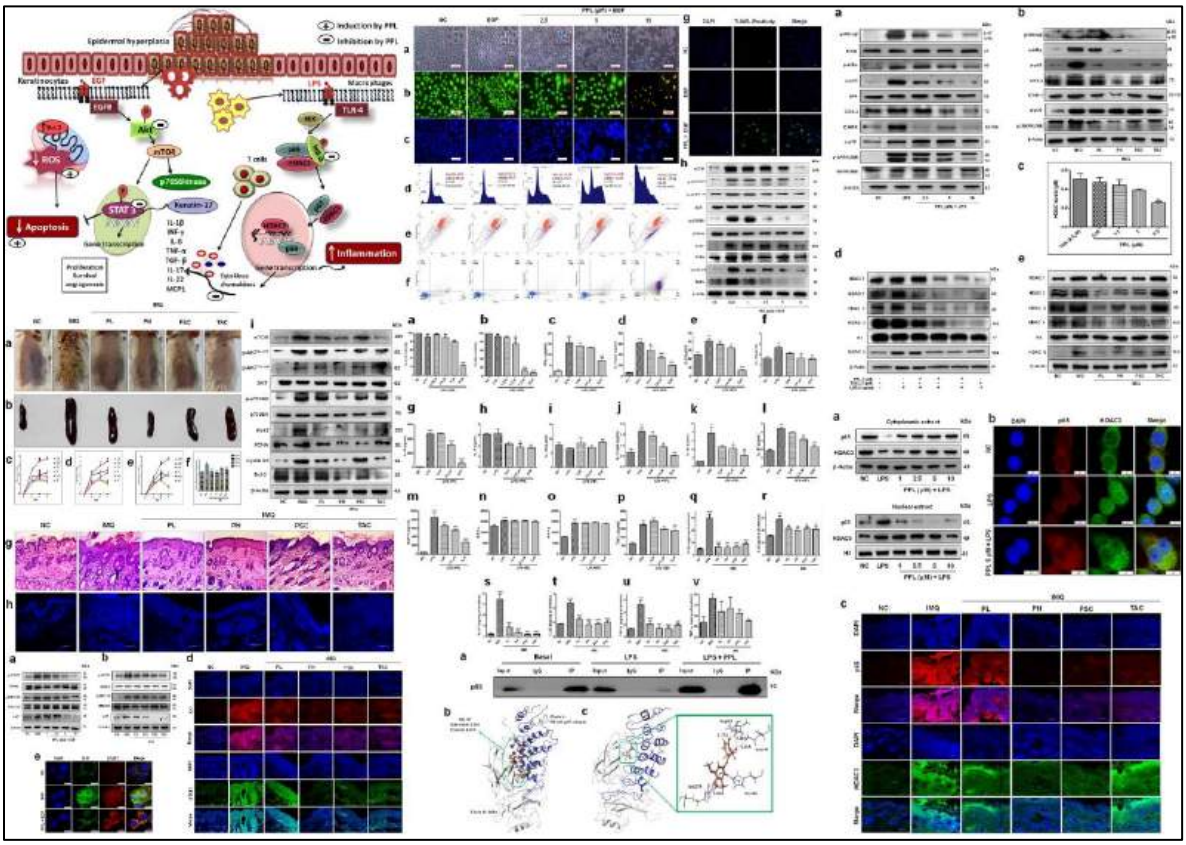


***Figure 3.***Piperlongumine Regulates Epigenetic Modulation and Alleviates Psoriasis-Like Skin Inflammation byInhibiting Hyperproliferation and Inflammation.

30/08/2024

**4 Nimbolide abrogates cerulein-induced chronic pancreatitis by modulating β-catenin/Smad in a sirtuin-dependent way. *Pharmacological Research*, 2020 (I.F: 9.1; Citations: 22)**

The study investigates the therapeutic potential of nimbolide, a bioactive compound from the neem tree, in treating cerulein-induced chronic pancreatitis (CP) in a mouse model. Nimbolide significantly alleviates the severity of CP, as demonstrated by reductions in pancreatic enzyme levels, such as amylase and lipase, and decreased collagen deposition in the pancreas. These findings suggest that nimbolide effectively reduces both inflammation and fibrosis, which are key factors in the progression of CP. Mechanistically, the study reveals that nimbolide exerts its protective effects through the modulation of the β-catenin/Smad signaling pathways, with a critical role played by the protein SIRT1 (silent information regulator 1). Nimbolide treatment led to the downregulation of β-catenin and Smad proteins, which are known to drive fibrogenesis and inflammation in CP. The activation of SIRT1 by nimbolide was shown to be essential for these effects, as inhibition of SIRT1 with nicotinamide or splitomicin diminished nimbolide's protective impact, underscoring the importance of this pathway in its therapeutic action. Histopathological analysis provided further evidence of nimbolide's efficacy, showing significant reductions in CP-associated changes such as inflammatory cell infiltration and acinar cell atrophy in treated mice. These results collectively highlight nimbolide's potential as a novel therapeutic agent for chronic pancreatitis, offering protection through a SIRT1-dependent mechanism that modulates key fibrogenic and inflammatory pathways as shown in Figure 4.

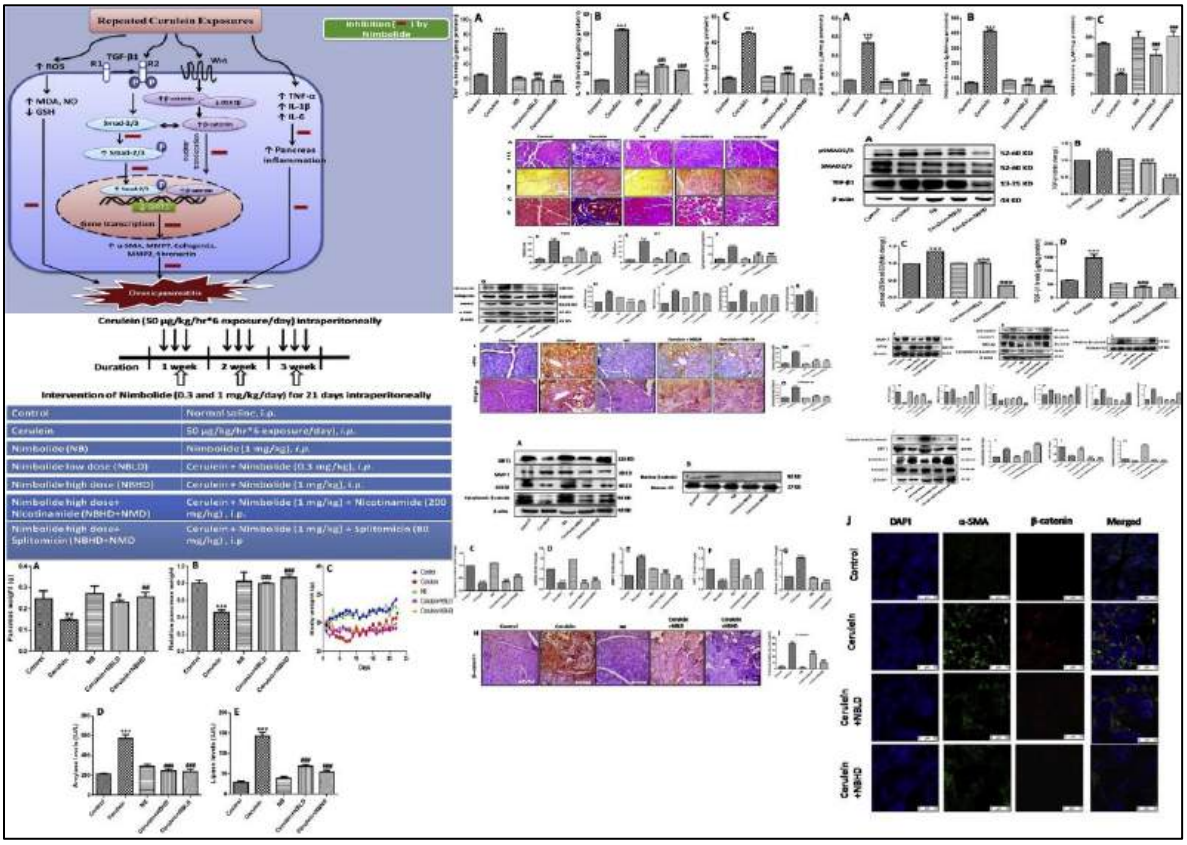


***Figure 4.***Nimbolide Abrogates Cerulein-Induced Chronic Pancreatitis by Modulating β-Catenin/Smad Pathways in a Sirtuin-Dependent Manner.

30/08/2024

## 5 AlgiMatrix™ Based 3D Cell Culture System as an In-Vitro Tumor Model for Anticancer Studies.

***Cancer Chemoprevention: Methods and Protocols*, 2016 (I.F: 2.9; Citations: 275)**

The study advances cancer research by developing a more physiologically relevant in vitro tumor model using AlgiMatrix™ scaffolds, which more accurately replicates the tumor microenvironment compared to traditional 2D cultures. This 3D culture model demonstrates significant advantages, particularly in mimicking the multicellular spheroid structure of tumors, which is crucial for studying drug resistance and tumor behavior in a more realistic context. The research highlights that drug resistance is notably higher in the 3D AlgiMatrix™ system, with IC50 values for anticancer drugs like Docetaxel significantly elevated in 3D cultures compared to 2D ones. For example, IC50 values for Docetaxel in 3D cultures ranged from 76.27 to 151.04 µM across different cancer cell lines, whereas in 2D cultures, these values were much lower, from 1.41 to 14.53 µM. The study also underscores the increased resistance of cancer stem cells (CSCs) in 3D cultures, which poses a significant challenge in chemotherapy due to their higher drug resistance compared to parental cells. Poor drug penetration within the 3D spheroids was identified as a contributing factor to this resistance, with only 10.52% of Doxorubicin penetrating the spheroids and limited uptake of nanoparticles. Additionally, the study observed reduced apoptosis in 3D cultures, with lower levels of cleaved caspase-3 and less impact on the anti-apoptotic marker Bcl-2, suggesting that 3D models better express drug resistance genes. The 3D tumor model's ability to grow spheroids in 96-well plates also makes it suitable for high-throughput drug screening, offering a more realistic and efficient approach to drug discovery as shown in Figure 5. This model holds potential for improving the accuracy of drug efficacy studies by providing a more relevant tumor environment.

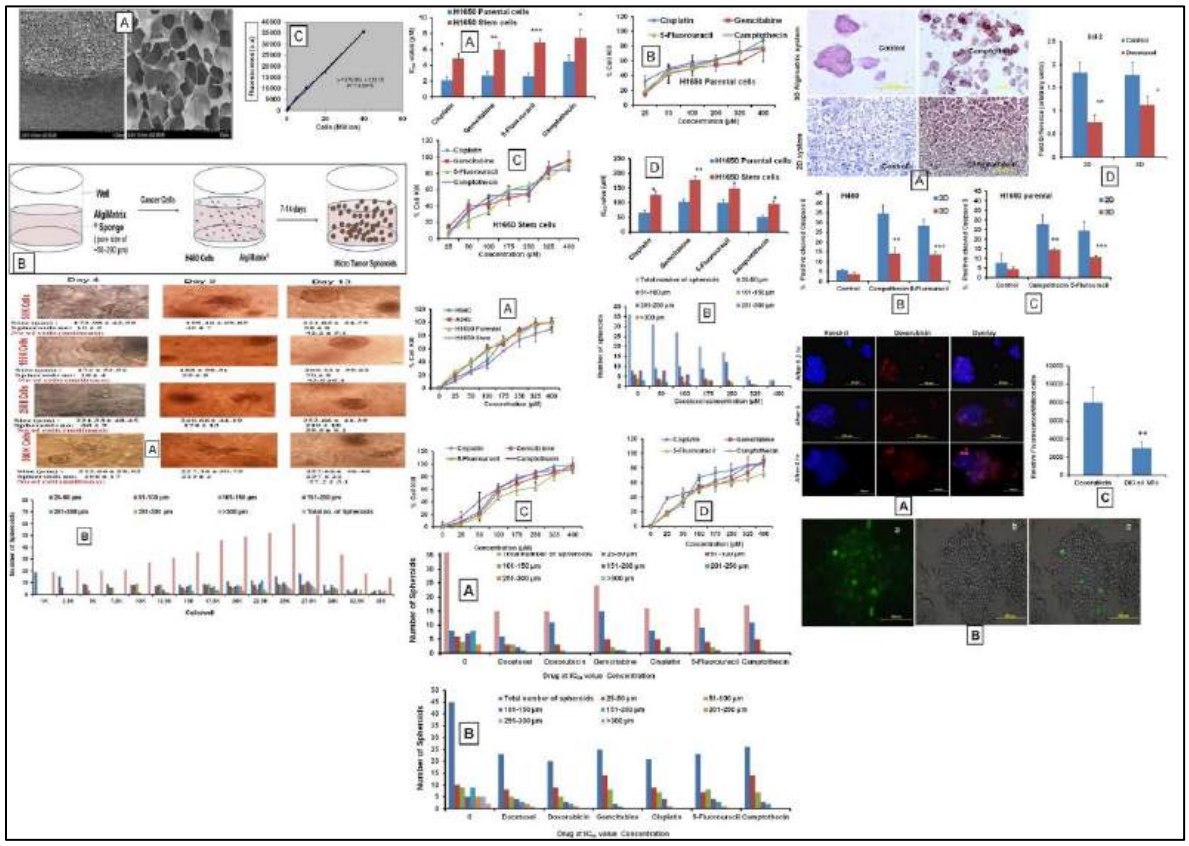

***Figure 5.*** AlgiMatrix™ Based 3D Cell Culture System as an In-Vitro Tumor Model for Anticancer Studies.

30/05/2024

**6 Withaferin-A attenuates multiple low doses of Streptozotocin (MLD-STZ) induced type 1 diabetes.*Biomedicine & Pharmacotherapy*, 2018 (I.F: 6.9; Citations: 84)**

The study presents compelling evidence for the therapeutic potential of Withaferin A (WA) in treating Type 1 diabetes mellitus (T1DM) using a mouse model induced by multiple low doses of Streptozotocin (MLD-STZ). WA treatment significantly lowered blood glucose levels in diabetic mice, with higher doses (10 mg/kg) reducing glucose levels from over 300 mg/dL to approximately 150 mg/dL, indicating a marked improvement in glucose regulation. Remarkably, only 25% of WA-treated mice developed diabetes, compared to a 100% incidence in untreated controls, suggesting WA's potential in preventing the onset of diabetes. Additionally, WA demonstrated strong antioxidant effects by decreasing oxidative stress markers, such as malondialdehyde (MDA) levels, by approximately 40%, and increasing glutathione (GSH) levels by over 50% in pancreatic tissues. The study also highlighted WA's anti-inflammatory properties, significantly reducing pro-inflammatory cytokines IL-6 and TNF-α. IL-6 levels were reduced from around 150 pg/mL to about 80 pg/mL, and TNF-α levels from approximately 250 pg/mL to 120 pg/mL in WA-treated mice. The research further showed that WA modulated key signaling pathways, increasing the nuclear translocation of Nrf2, a critical regulator of the antioxidant response, while decreasing NFκB activity, which is linked to inflammation. These changes were statistically significant, underscoring WA's role in reducing inflammation. Finally, WA treatment reduced apoptosis markers in pancreatic tissues, with a 60% decrease in TUNEL-positive cells, indicating less DNA fragmentation and cell death. Overall, these findings suggest that WA has substantial potential as a therapeutic agent for managing T1DM by addressing both the inflammatory and oxidative stress components of the disease as shown in Figure 6.

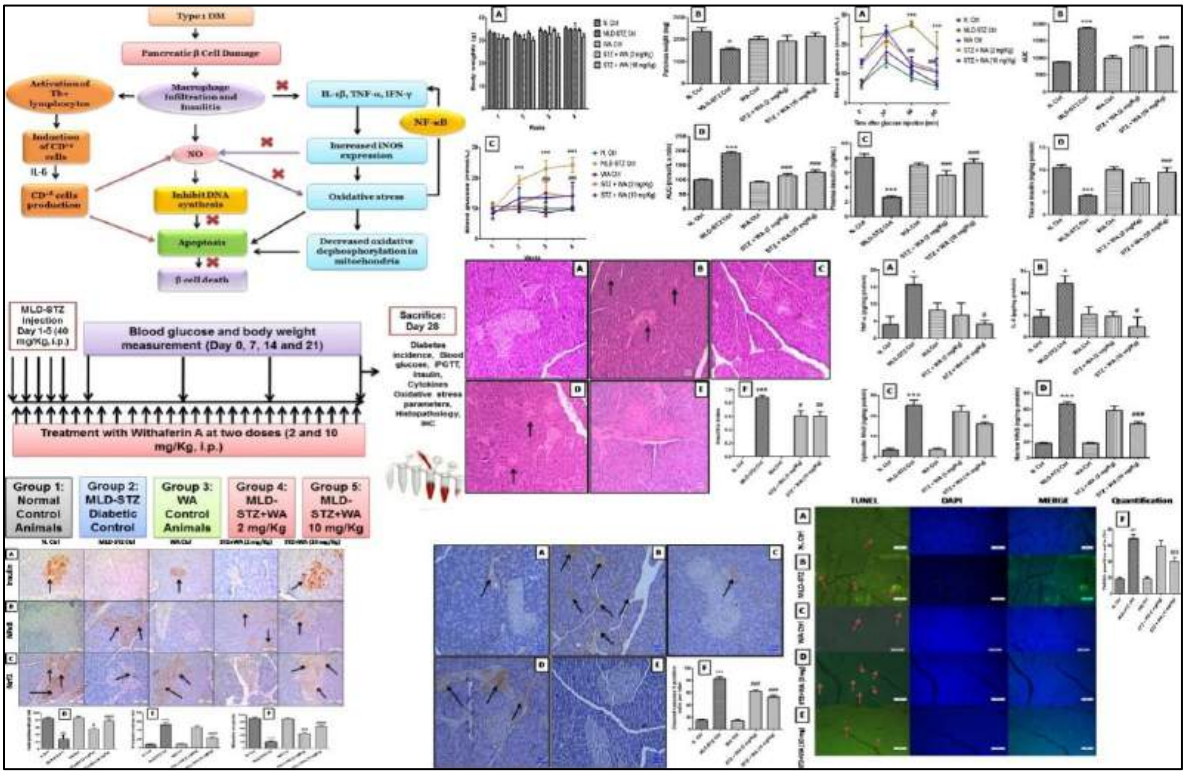


***Figure 6.***Withaferin-A Attenuates Multiple Low Doses of Streptozotocin (MLD-STZ) Induced Type 1 Diabetes.

30/05/2024

**7 Selenium nanoparticles produce a beneficial effect in psoriasis by reducing epidermalhyperproliferation and inflammation.*Journal of Nanobiotechnology, 2021*(I.F: 10.6; Citations: 33)**

The research explores selenium nanoparticles (SeNPs) as a novel treatment for psoriasis, a chronic autoimmune condition characterized by excessive keratinocyte growth and inflammation. Current therapies often come with adverse effects, making SeNPs a promising alternative. The study demonstrates that SeNPs induce apoptosis in keratinocytes by generating reactive oxygen species (ROS) and causing cell cycle arrest, effectively addressing the root causes of psoriatic lesions. In vivo experiments using a mouse model of psoriasis (IMQ-induced) showed that topical SeNP application significantly reduced psoriasis severity, improved skin condition, and decreased splenomegaly, reflecting the nanoparticles' effectiveness in a model that closely mimics human psoriasis. As shown in Figure 7 Molecular analysis further revealed that SeNPs modulate key signaling pathways involved in psoriasis, including MAPKs, STAT3, GSK-3β, and Akt, as well as markers like PCNA, Ki67, and cyclin-D1, all of which are critical in inflammation and keratinocyte proliferation. This multifaceted action underscores SeNPs' potential as a comprehensive therapeutic option. The study also highlights the safety of SeNPs, suggesting that they are a less toxic alternative to current treatments, which is particularly important for long-term management. The detailed characterization of SeNPs, including their size, morphology, and stability, further supports their potential for reproducibility and future development in psoriasis therapy.

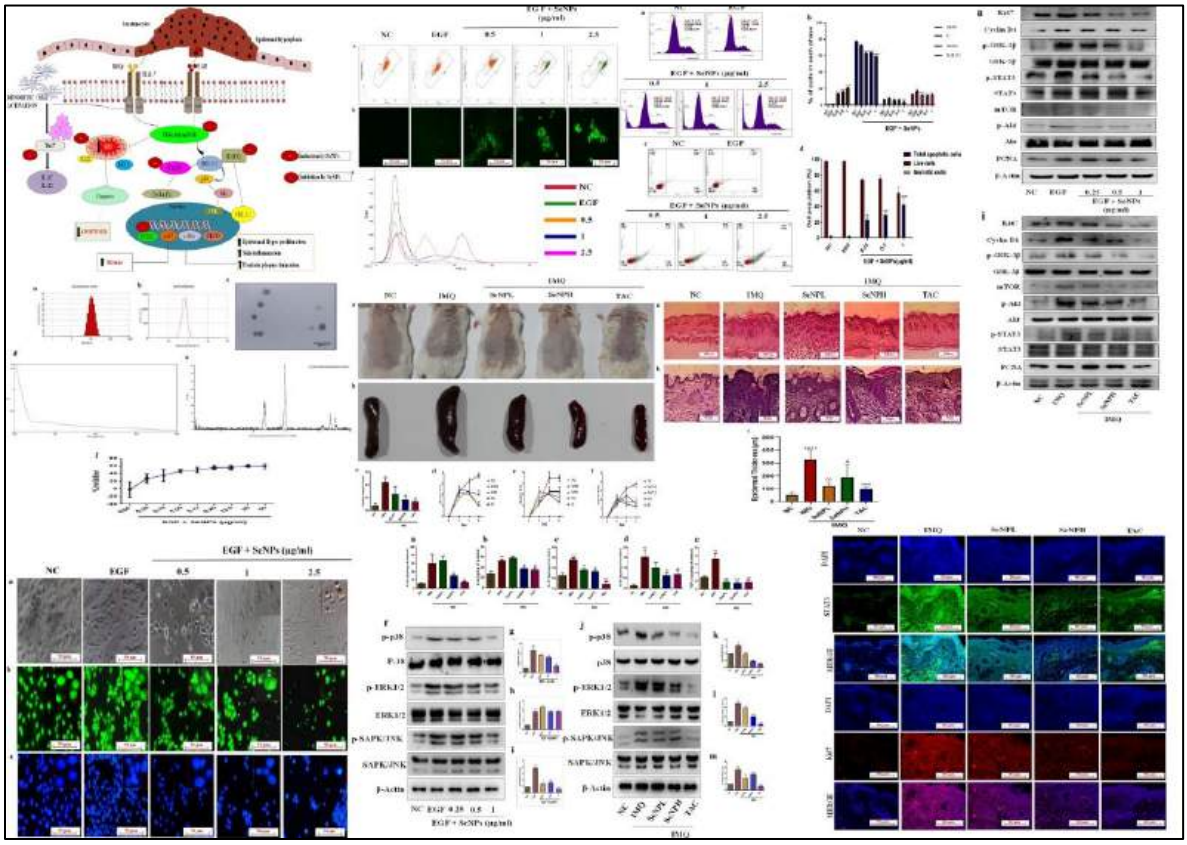

***Figure 7.***Selenium Nanoparticles Produce a Beneficial Effect in Psoriasis by Reducing Epidermal Hyperproliferation and Inflammation.

30/05/2024

**8 Approaches to improve the oral bioavailability and effects of novel anticancer drugsberberine and betulinic acid. *PloS one*, 2014 (I.F: 2.9; Citations: 146)**

The research presents significant advancements in enhancing the oral bioavailability and anticancer efficacy of the drugs Berberine (BBR) and Betulinic acid (BA), both limited by poor bioavailability. The study introduces a novel formulation approach using spray-dried (SD) mucoadhesive microparticles, produced with dual-channel spray gun technology. This method effectively improves the oral absorption of BBR and BA, addressing a major limitation in their clinical application. As demonstrated by pharmacokinetic studies, the SD formulations resulted in a marked increase in oral bioavailability. For BBR, there was a 3.46-fold increase in plasma Cmax concentration, while BA showed a 3.90-fold increase. The area under the curve (AUC) levels for BBR and BA were enhanced by 6.98-fold and 7.41-fold, respectively, indicating a substantial improvement in systemic exposure. In addition to enhanced bioavailability, the SD formulations exhibited superior anticancer effects. In A549 orthotopic and H1650 metastatic non-small cell lung cancer (NSCLC) models, the SD formulations significantly reduced tumor volumes—49.8% for BBR and 53.4% for BA. The study also explored the molecular mechanisms underlying these effects. BBR in its SD form reduced the expression of survivin, Bcl-2, cyclin D1, MMP-9, HIF-1a, and VEGF while increasing the expression of cleaved caspase 3, p53, and TUNEL. Similarly, BA SD formulations enhanced the expression of apoptotic markers such as p38, Phospho-JNK, Bax, BAD, and cleaved caspase 3&8. Importantly, chronic administration of these SD formulations did not produce any observable toxicity, indicating a favorable safety profile. The findings suggest that the spray-drying technique holds promise as a superior method for the oral delivery of BBR and BA, paving the way for their potential clinical application in cancer therapy as shown in Figure 8.

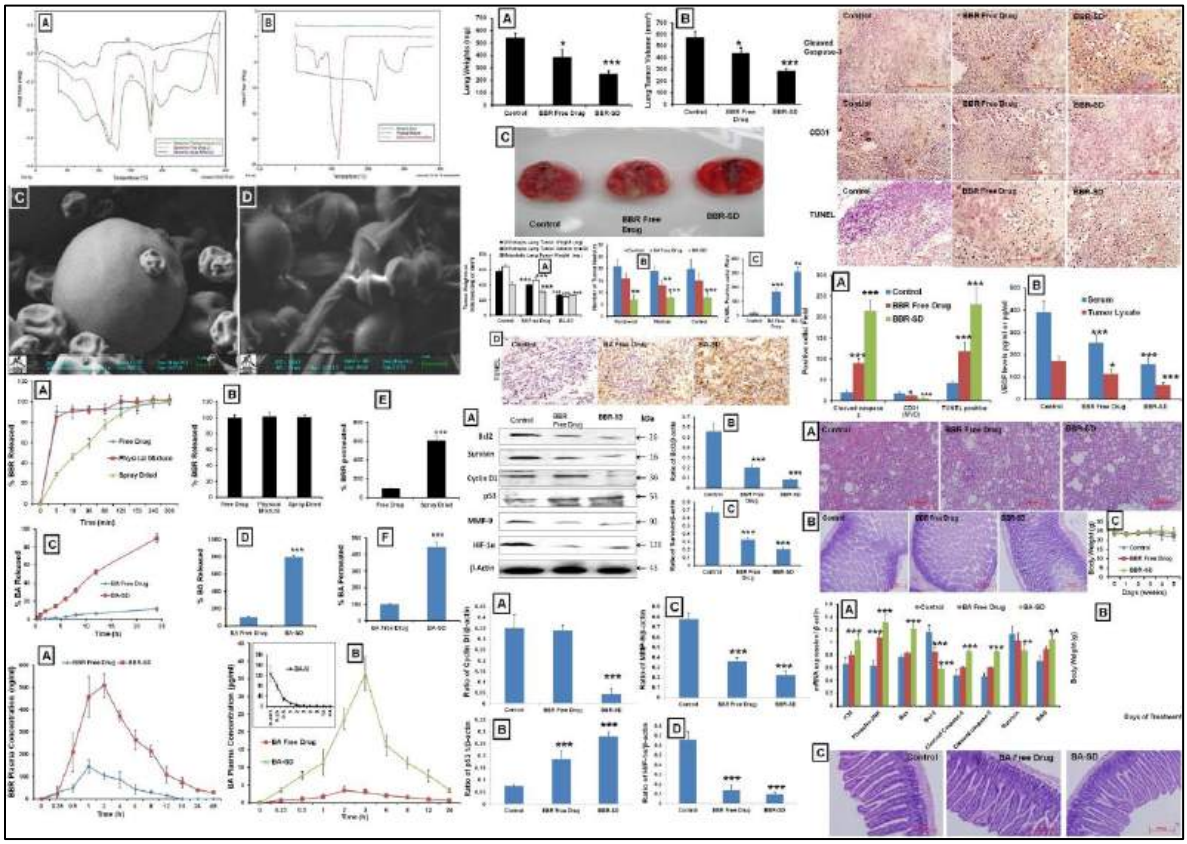

***Figure 8.***Approaches to Improve the Oral Bioavailability and Effects of Novel Anticancer Drugs Berberine and Betulinic Acid.

30/05/2024

**9 Nanoceria suppresses multiple low doses of streptozotocin-induced Type 1 diabetes by inhibition of Nrf2/NF-κB pathway and reduction of apoptosis. *Nanomedicine*, 2018 (I.F: 4.2; Citations: 72)**

The research highlights the therapeutic potential of nanoceria (NC) in treating Type 1 diabetes mellitus (T1DM), particularly through its antioxidant, anti-inflammatory, and anti-apoptotic properties. This study is the first to demonstrate that NC can significantly suppress the onset of diabetes in a MLD-STZ-induced T1DM mouse model. Treatment with NC at doses of 0.2 and 2 mg/kg reduced diabetes incidence to 50% and 37.5%, respectively. Furthermore, NC administration led to a substantial reduction in blood glucose levels and improved glucose clearance, especially at the higher dose.The study also underscores NC's role in modulating oxidative and nitrosative stress, as evidenced by decreased tissue levels of malondialdehyde (MDA) and nitric oxide (NO) and increased glutathione (GSH) levels. These findings suggest that NC has potent antioxidant and free radical scavenging activities, crucial in managing T1DM. Additionally, NC treatment significantly attenuated pro-inflammatory cytokines TNF-α and IL-6 in pancreatic tissue, highlighting its anti-inflammatory potential (as shown in Figure 9).NC's ability to restore insulin levels was another key finding, with treated mice showing significant improvement in both plasma and pancreatic insulin levels, indicating protection of pancreatic β-cells. Histological analysis further confirmed the ameliorative effects of NC on pancreatic islet morphology, with a marked reduction in insulitis severity. The study also revealed that NC enhances Nrf2 expression while suppressing NF-κB expression, suggesting a mechanism by which NC protects against T1DM. Additionally, NC exhibited superoxide dismutase 1 (SOD1) mimetic activity and reduced apoptosis in pancreatic β-cells, as indicated by lower levels of cleaved caspase-3 and fewer TUNEL-positive cells.

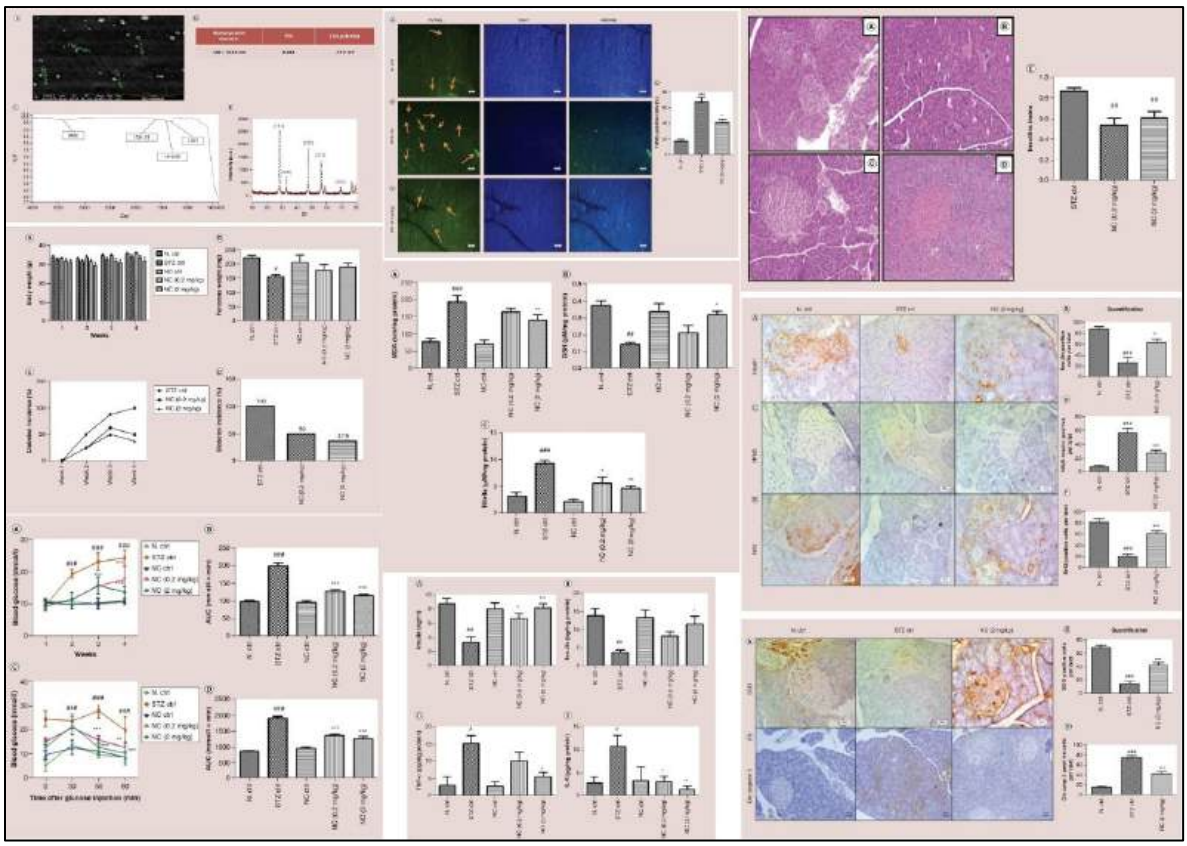

***Figure 9.***Nanoceria Suppresses Multiple Low Doses of Streptozotocin-Induced Type 1 Diabetes by Inhibition of Nrf2/NF-κB Pathway and Reduction of Apoptosis.

30/05/2024

**10 iRGD conjugated nimbolide liposomes protect against endotoxin-induced acute respiratory distress syndrome.** ***Nanomedicine: Nanotechnology, Biology and Medicine*****, 2021 (I.F: 4.2; Citations: 17)**

This study advances nanomedicine by developing a novel drug delivery system, iRGD-NIMLip, for treating Acute Respiratory Distress Syndrome (ARDS) and cytokine storms related to COVID-19. The system conjugates nimbolide, an anti-inflammatory compound, with liposomes and the iRGD peptide to enhance targeting and efficacy. The research successfully synthesized iRGD-NIMLip, a combination of nimbolide with liposomes and the iRGD peptide, improving lung inflammation targeting compared to the free drug or liposomes without the peptide. The study demonstrated that iRGD-NIMLip significantly inhibits the expression of key inflammatory proteins such as p65 NF-κB, Akt, MAPK, Integrin β3 and β5, STAT3, and DNMT1, which play crucial roles in the inflammatory response to endotoxins like LPS. The liposomal formulation addressed the poor pharmacokinetics of the free drug, leading to enhanced targeting and effectiveness in treating lung inflammation. The research highlighted iRGD-NIMLip's potential in protecting against severe outcomes in ARDS and the cytokine storm associated with COVID-19. Both in vitro and in vivo experiments using LPS-induced ARDS models validated the protective effects of iRGD-NIMLip against lung inflammation and oxidative stress (as shown in Figure 10). Characterization of the liposomes revealed a particle size of 171.5 nm and an 85.24% entrapment efficiency of nimbolide. In vivo studies showed that iRGD-NIMLip treatment significantly reduced lung weight index, inflammatory cell counts, and levels of pro-inflammatory cytokines in bronchoalveolar lavage fluid (BALF), underscoring its therapeutic potential in managing severe lung inflammation and related conditions.

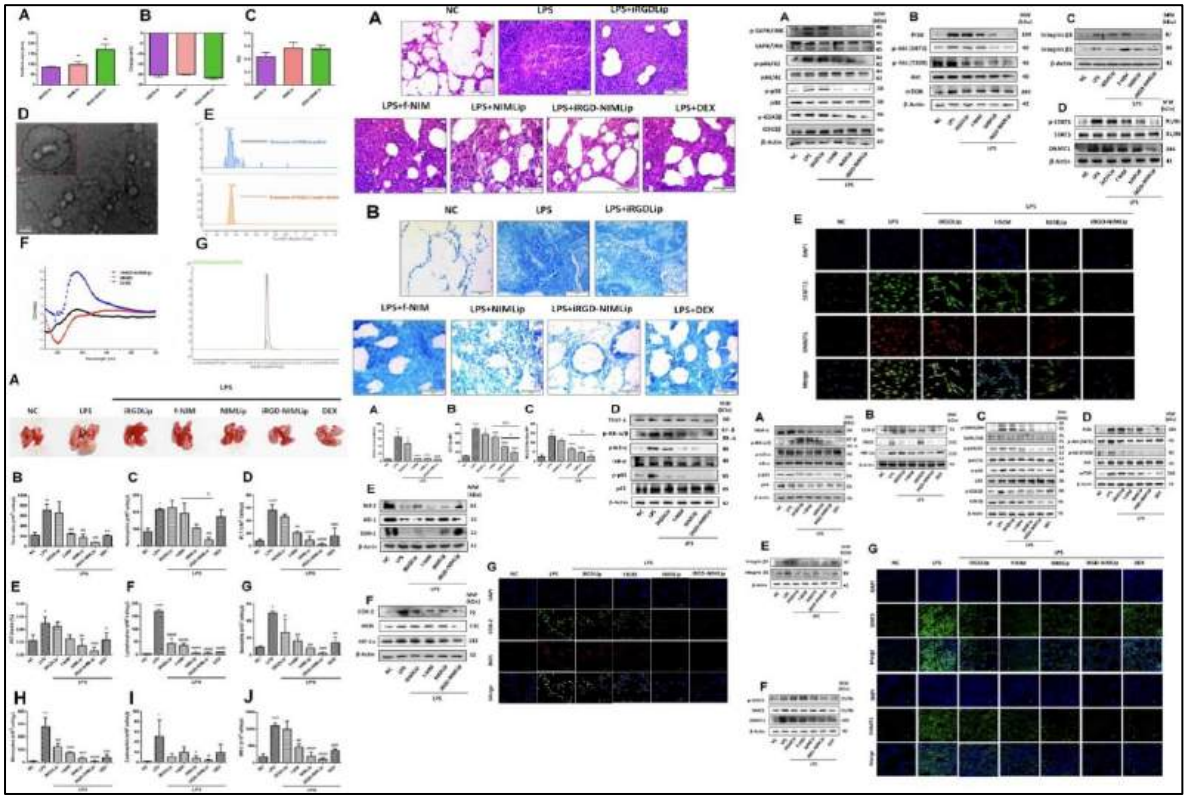


***Figure 10.***iRGD-Conjugated Nimbolide Liposomes Protect Against Endotoxin-Induced Acute Respiratory Distress Syndrome.

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