Fig. S1. Transcriptional RNA analysis of DEGs characterizes a distinct signature associated with ROS production and autophagy in lupiwighteone-treated HCC cells. (A) PCA analysis of Huh-7 and Hep3B cells in lupiwighteone-treated and -untreated group. **(B-C)** Volcano plots of DEGs in Huh-7 **(B)** and Hep 3B **(C)** cells following lupiwighteone incubation. Red: upregulated genes; Blue: downregulated genes; Black: non-significantly changed genes. The vertical dashed lines represent $|\log_2 FoldChange| = 1$, and the horizontal dashed line represents a p-value = 0.05. **(D-E)** Expression profiles of genes associated with ROS production and autophagy in Huh-7 **(D)** and Hep3B **(E)** cells. The color gradient represents the statistical significance based on *p*-values, where red indicating lower *p*-values and higher significance.

Fig. S2. Molecular docking and transcriptomic analysis of potential downstream targets of lupiwighteone. (A-F) Molecular docking analysis of lupiwighteone with six key predicted target proteins including HSP90AA1, CASP3, AKT1, BCL2, ALB and EGFR. The 3D binding modes (upper panels) and 2D interaction diagrams (lower right panels) are shown, with binding affinity

values (kcal/mol) indicated. **(G-H)** Transcriptional RNA analysis of the expression levels of the 6 target proteins in Huh-7 **(G)** and Hep 3B **(H)** cells in the control and lupiwighteone-treated group.

Fig. S3. Transcriptional RNA analysis of DEGs reveals significant enrichment of the MAPK signaling pathway. (A) Venn diagram showing the overlap of DEGs between Huh-7 and Hep 3B cells after lupiwighteone exposure. **(B-C)** KEGG pathway enrichment analysis of DEGs derived from Huh-7 **(B)** and Hep 3B **(C)** cells. The MAPK signaling pathway is highlighted as a core enriched signaling pathway. The color gradient represents the variation of p-values, and the dot size represents the total number of enriched genes in each pathway. The above data were expressed as mean±SD; n=3; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Control: lupiwighteone untreated group.

Fig. S4. Synthetic workflow for the preparation of NP@Lup nanopaticles. (A) Schematic diagram depicting the step-by-step preparation of NP@Lup via the nanoprecipitation method. **(B)** Observations of precipitation behaviors in NP@Lup nanoparticle suspensions prepared under different conditions. **(C)** The step-by-step extraction of Hep3B hepatocellular carcinoma cell membranes with a commercial cell membrane isolation kit.