

Comparative Pharmacokinetic–Pharmacodynamic Evaluation of L-Theanine and L-Leucine Polymeric Nanoparticles in a Paracetamol-Induced Hepatic Injury Model

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Abstract



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Background: Polymeric nanoparticle systems can modify the disposition and release characteristics of bioactive molecules and may improve their biological performance. The present work compared the in-vivo pharmacokinetic and hepatoprotective responses of optimized L-theanine- and L-leucine-loaded polymeric nanoparticles. **Methods:** Optimized formulations LT-SE-PN4 and LL-SE-PN4, prepared by the solvent evaporation approach, were selected for in-vivo evaluation. Their reported particle sizes were 127.21 ± 1.11 nm and 126.11 ± 1.09 nm, respectively, with entrapment efficiencies of $85.17 \pm 0.30\%$ and $81.37 \pm 0.80\%$. Pharmacokinetic profiles were assessed following oral administration in albino rats. Hepatic effects were evaluated using serum AST, ALT, ALP and bilirubin, absolute liver weight and histopathological examination in a paracetamol-associated hepatic injury model. **Results:** LT-SE-PN4 produced a C_{max} of 1.54 ± 0.42 µg/mL at 4 ± 0.08 h, whereas LL-SE-PN4 produced a C_{max} of 2.98 ± 0.74 µg/mL at 2 ± 0.06 h. Reported AUC_{0–24} values were 22.36 ± 2.21 and 41.56 ± 2.78 µg/mL·h, with relative bioavailability values of 319.92% and 320.91%, respectively. Disease-control animals showed increased AST, ALT, ALP, bilirubin and absolute liver weight. Both nanoparticle-treated groups showed biochemical values closer to the normal-control group and comparatively preserved liver histology. **Conclusion:** The present work derived in-vivo findings demonstrate a consistent association between nanoparticle administration, altered systemic exposure and improved biochemical and histological indices in the experimental hepatic injury model. The findings support further controlled pharmacokinetic, mechanistic, toxicological and translational studies of these formulations.

Keywords: L-theanine; L-leucine; polymeric nanoparticles; pharmacokinetics; hepatoprotection; paracetamol; liver injury; bioavailability.

INTRODUCTION

The liver is a central organ in xenobiotic metabolism, nutrient homeostasis, antioxidant defense, and biotransformation of therapeutic agents. Because of its continuous exposure to endogenous and exogenous chemicals, the liver is particularly vulnerable to oxidative, inflammatory, and metabolic insults. Drug-induced liver injury remains an important challenge in experimental and clinical pharmacology, and excessive exposure to paracetamol (acetaminophen; APAP) represents one of the most extensively characterized models of acute hepatotoxicity.^{1–2} At therapeutic doses, paracetamol is predominantly converted into non-toxic glucuronide and sulfate conjugates; however, a small fraction undergoes cytochrome P450-mediated oxidation, particularly through CYP2E1, to generate the highly reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI).³ Under normal conditions, NAPQI is rapidly neutralized through conjugation with reduced glutathione (GSH). Following excessive paracetamol

exposure, increased NAPQI formation and depletion of hepatic GSH allow covalent modification of cellular and mitochondrial proteins, initiating oxidative stress, mitochondrial dysfunction and hepatocellular injury.^{3–4} The pathophysiology of paracetamol-induced hepatic injury extends beyond simple depletion of glutathione. Protein adducts formation, mitochondrial oxidant stress, activation of c-Jun N-terminal kinase (JNK), mitochondrial permeability transition, ATP depletion, reactive nitrogen species formation and subsequent necrotic cell death constitute interconnected events in the progression of hepatic injury.⁵ The early oxidative disturbance also stimulates endogenous antioxidant responses, including nuclear factor erythroid 2-related factor 2 (Nrf2)-dependent pathways involved in restoration of glutathione and other cytoprotective enzymes.⁵ Consequently, experimental interventions capable of maintaining intracellular antioxidant capacity, limiting excessive oxidative stress, preserving mitochondrial function and suppressing inflammatory signaling may provide protection against paracetamol-

associated hepatic injury.⁵ Amino acids and amino-acid-derived bioactive compounds have attracted increasing attention as potential modulators of oxidative stress, inflammation, cellular metabolism and tissue repair. Among these, L-theanine (γ -glutamylethylamide) is a naturally occurring non-protein amino acid predominantly associated with *Camellia sinensis*. Although widely investigated for neurobiological and nutritional effects, accumulating experimental evidence indicates that L-theanine can influence hepatic antioxidant and inflammatory pathways.⁶ Experimental studies have demonstrated that L-theanine administration can increase hepatic glutamate availability and support glutathione homeostasis, providing a mechanistic basis for its potential cytoprotective activity.⁷ In animal models of chemically induced hepatic injury, L-theanine has been associated with reductions in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), lipid peroxidation and inflammatory mediators, together with preservation of hepatic GSH and antioxidant enzyme activities.⁸

The hepatoprotective potential of L-theanine has been demonstrated across different experimental injury models. In carbon tetrachloride-induced acute liver injury, L-theanine reduced elevations in ALT, AST and bilirubin and attenuated lipid peroxidation and depletion of hepatic GSH. The study further suggested suppression of CYP2E1-mediated metabolic activation and reduction of downstream inflammatory and apoptotic responses.⁸ Similarly, experimental studies of alcohol-induced hepatic injury have reported preservation of antioxidant capacity, inhibition of reactive oxygen species generation and attenuation of mitochondrial and apoptotic changes following L-theanine administration.⁹ More recent investigations have linked L-theanine-mediated protection against chemically induced hepatic oxidative injury with modulation of Nrf2 signaling and glutathione homeostasis.¹⁰ These observations provide a biologically plausible foundation for evaluating L-theanine as a protective molecule in paracetamol-induced hepatic injury, although the extent to which such activity can be enhanced through nanoparticle-based delivery remains insufficiently characterized. L-leucine, in contrast, is an essential branched-chain amino acid (BCAA) with important nutritional and metabolic functions. Together with L-isoleucine and L-valine, leucine participates in protein turnover, energy metabolism and intracellular signaling. BCAAs have attracted considerable interest in hepatic disorders because liver disease is frequently accompanied by disturbances in amino-acid metabolism, altered BCAA utilization and changes in the circulating BCAA-to-aromatic-amino-acid ratio.^{11,12} Leucine is also a recognized nutritional signal capable of influencing protein synthesis and mechanistic target of rapamycin (mTOR)-associated pathways.^{11,13} These properties have prompted investigation of BCAA supplementation in liver disease, particularly in relation to nutritional status, hepatic regeneration and complications associated with chronic hepatic dysfunction.¹³

Nevertheless, the biological role of L-leucine in liver injury is more complex than that of a conventional antioxidant. Evidence concerning BCAA supplementation in hepatic disorders is heterogeneous, and reported outcomes depend on the type and severity of liver disease, nutritional status, treatment duration and composition of the amino-acid preparation.^{14,15} Recent reviews emphasize that BCAA supplementation can influence protein metabolism, ammonia handling and cellular signaling, but its effects on liver function are not uniformly demonstrated. Thus, direct comparison of L-leucine with L-theanine in a controlled acute hepatic injury model is scientifically relevant because the two compounds represent distinct biochemical approaches: L-theanine is associated with antioxidant and anti-inflammatory responses, whereas L-leucine primarily represents an essential amino-acid and metabolic-signaling strategy.

Despite their different biological characteristics, the therapeutic performance of both molecules may be constrained by conventional administration. Nanotechnology offers an opportunity to modify the disposition and biological exposure of bioactive compounds through controlled release, protection from degradation and altered tissue distribution. Polymeric nanoparticles can provide a nanoscale carrier environment capable of modifying absorption, release kinetics, systemic exposure and interaction with biological barriers.^{16,17} In oral delivery, nanoparticulate systems may additionally protect encapsulated compounds from unfavorable gastrointestinal conditions and can influence residence time and absorption processes.^{17,18} Such characteristics are particularly important when pharmacological effects depend not only on the intrinsic activity of a molecule but also on the magnitude and duration of its exposure. The integration of pharmacokinetic and pharmacodynamic assessment is therefore essential for understanding whether nanoparticle formulation translates into meaningful biological improvement. Pharmacokinetic parameters such as maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration–time curve (AUC), elimination half-life and mean residence time provide information regarding systemic exposure and disposition. Pharmacodynamic measurements, including serum ALT, AST, alkaline phosphatase (ALP), bilirubin, hepatic oxidative-stress markers and histopathological changes, provide complementary evidence of functional and structural protection. A comparative PK–PD approach can consequently establish whether differences in hepatic protection correspond with differences in systemic exposure and duration of action rather than relying solely on endpoint biochemical measurements. Paracetamol-induced hepatic injury provides a well-established experimental platform for such investigation because the model incorporates metabolic activation, glutathione depletion, oxidative stress, mitochondrial injury and inflammatory amplification.¹⁵ The use of this model also permits simultaneous assessment of biochemical, histopathological and pharmacokinetic outcomes.

Within this framework, comparison of L-theanine-loaded and L-leucine-loaded polymeric nanoparticles can provide insight into how two chemically and biologically distinct amino-acid-based agents perform when delivered through the same nanocarrier strategy. Accordingly, the present study was designed to comparatively evaluate the pharmacokinetic and pharmacodynamic performance of L-theanine and L-leucine polymeric nanoparticles in a paracetamol-induced hepatic injury model. The study focuses on determining whether nanoparticle formulation modifies systemic exposure and whether these pharmacokinetic changes are accompanied by improvements in biochemical indicators of hepatic injury, antioxidant status and liver morphology. Such an integrated evaluation may help clarify the relationship between nanoparticle-mediated delivery, systemic disposition and hepatoprotective response, while providing comparative evidence for the further development of amino-acid-based nanotherapeutic strategies for acute hepatic injury.

MATERIALS AND METHODS

Optimized polymeric nanoparticle formulations

LT-SE-PN4 and LL-SE-PN4 were the optimized formulations selected from the formulation-development program. The formulations were prepared by the solvent evaporation technique. LT-SE-PN4 showed a particle size of 127.21 ± 1.11 nm, zeta potential of -24.21 ± 1.09 mV and entrapment efficiency of $85.17 \pm 0.30\%$. LL-SE-PN4 showed a particle size of 126.11 ± 1.09 nm, zeta potential of -24.81 ± 1.19 mV and entrapment efficiency of $81.37 \pm 0.80\%$. Transmission electron microscopy in the present work showed spherical and relatively uniform particles.¹⁶

In-vivo experimental design

The pharmacokinetic and hepatoprotective investigations were performed in albino rats as reported in the present work. Seven experimental groups were used, with six animals/observations per group for the reported biochemical and liver-weight datasets: Group I, normal control; Group II, disease control; Group III, standard treatment; Group IV, L-theanine; Group V, LT-SE-PN4; Group VI, L-leucine; and Group VII, LL-SE-PN4. Silymarin was used as the standard hepatoprotective treatment.

The disease model was described in the present work as paracetamol-associated hepatotoxicity. The retrieved present work sections did not provide a sufficiently clear, validated record of the exact paracetamol dose/regimen or the institutional animal-ethics approval number. These details should therefore be inserted from the approved animal protocol and laboratory records before journal submission rather than inferred or reconstructed.

Pharmacokinetic evaluation

Following oral administration, plasma drug concentrations were determined at the reported sampling times of 1, 2, 4, 6, 8, 10, 12 and 14 h. The present work reported concentration–time values for LT-SE-PN4 and LL-SE-PN4 and calculated C₁, AUC_{0–24}, C_{max}, T_{max} and relative bioavailability. The concentration–time profiles were reproduced from the present work dataset in Figure 1¹⁷.

Biochemical assessment

Blood was collected through the retro-orbital plexus into heparinized tubes and centrifuged at 3000 rpm for 10 min to obtain plasma. Biochemical analysis was performed using an automated analyzer (ERBA Diagnostic Mannheim GmbH; CHEM-7) according to the procedures described in the present work. AST and ALT were assessed using the dinitrophenylhydrazine-based method, while ALP was assessed using a phenyl-phosphate-based procedure. Serum bilirubin was also evaluated. The resulting values were expressed as mean $\pm$ SD.¹⁸

Absolute liver weight and histopathology

Absolute liver weight was recorded for each experimental group. For histopathological evaluation, liver tissues were processed using the protocol described in the present work, including fixation, paraffin embedding, sectioning and hematoxylin and eosin staining. The original histopathological composite supplied in the present work is reproduced as Figure 5 without modification to the tissue content.¹⁹

Statistical analysis

The present work reports one-way analysis of variance followed by the Newman–Keuls multiple comparison procedure, with $P < 0.05$ considered statistically significant. The present manuscript retains that statistical framework and reports the present work-derived means and standard deviations. Because individual animal-level observations were not available in the retrieved material, no new inferential statistics were calculated from the summary means.²⁰

RESULTS

Pharmacokinetic profile

The plasma concentration–time data demonstrated distinct exposure profiles for the two optimized nanoparticle formulations. LT-SE-PN4 increased from 0.5 $\mu\text{g/mL}$ at 1 h to a reported maximum concentration of 1.54 ± 0.42 $\mu\text{g/mL}$ at 4 ± 0.08 h. LL-SE-PN4 showed higher concentrations at the early sampling points, reaching 3.1 $\mu\text{g/mL}$ at 2 h in the reported concentration dataset and a calculated C_{max} of 2.98 ± 0.74 $\mu\text{g/mL}$ at 2 ± 0.06 h. The reported AUC_{0–24} was 22.36 ± 2.21 $\mu\text{g/mL}\cdot\text{h}$ for LT-SE-PN4 and 41.56 ± 2.78 $\mu\text{g/mL}\cdot\text{h}$ for LL-SE-PN4. Relative bioavailability values were 319.92% and 320.91%, respectively.

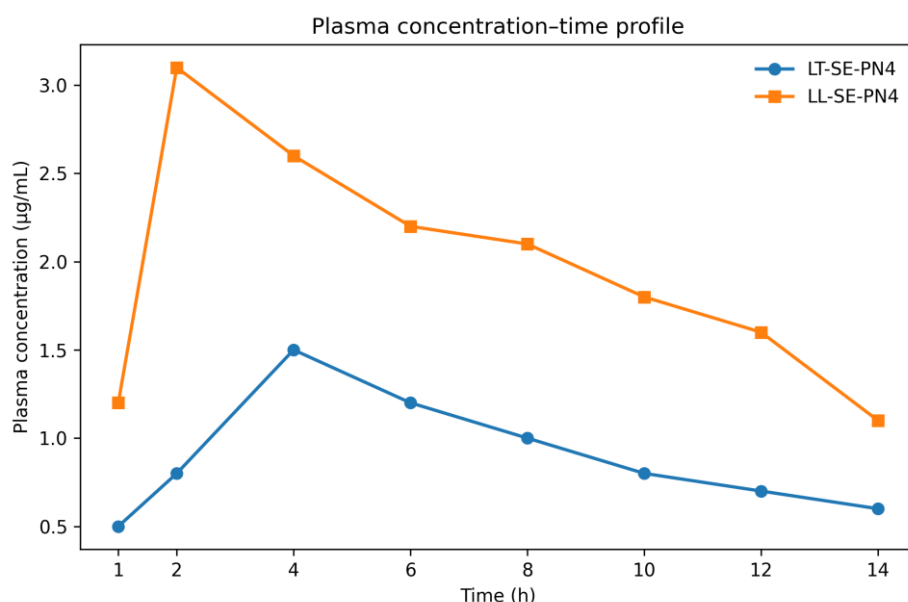


Figure 1. Plasma concentration-time profiles of LT-SE-PN4 and LL-SE-PN4 following oral administration. The plotted points reproduce the concentration values reported in the present work.

Hepatic biochemical markers

The disease-control group showed higher hepatic enzyme activities than the normal-control group. AST increased from 110.16 ± 5.38 IU/L in normal controls to 205.34 ± 7.04 IU/L in disease controls. ALT increased

from 60.89 ± 2.26 to 123.64 ± 3.36 IU/L, while ALP increased from 235.76 ± 8.97 to 405.62 ± 7.65 IU/L. LT-SE-PN4 and LL-SE-PN4 produced values of 111.16 ± 7.78 and 113.16 ± 7.78 IU/L for AST, 61.96 ± 2.78 and 62.96 ± 2.78 IU/L for ALT, and 279.48 ± 10.83 and 274.48 ± 10.83 IU/L for ALP, respectively.

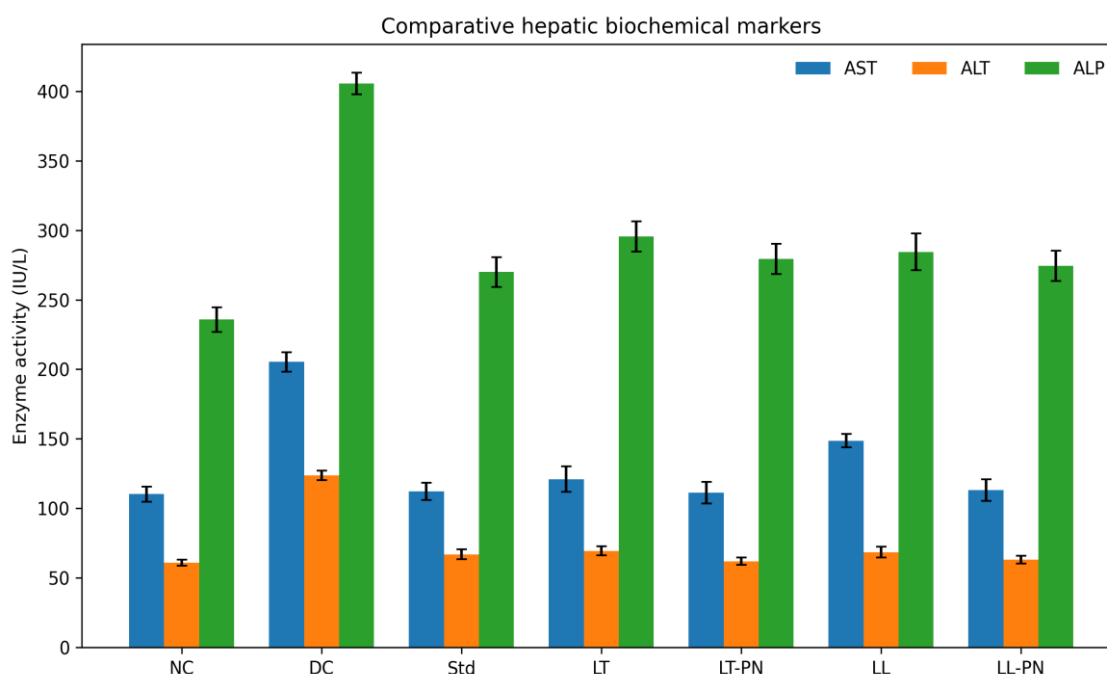


Figure 2. Comparative AST, ALT and ALP profiles across the experimental groups. Values are mean $\pm$ SD, $n = 6$, as reported in the present work. NC, normal control; DC, disease control; Std, standard; LT, L-theanine; LT-PN, LT-SE-PN4; LL, L-leucine; LL-PN, LL-SE-PN4.

Serum bilirubin

Serum bilirubin was 0.35 ± 0.019 mg/dL in the normal-control group and increased to 0.70 ± 0.037 mg/dL in

the disease-control group. The standard, L-theanine, LT-SE-PN4, L-leucine and LL-SE-PN4 groups showed values of 0.38 ± 0.016 , 0.40 ± 0.014 , 0.35 ± 0.019 , 0.43 ± 0.018 and 0.36 ± 0.019 mg/dL, respectively.

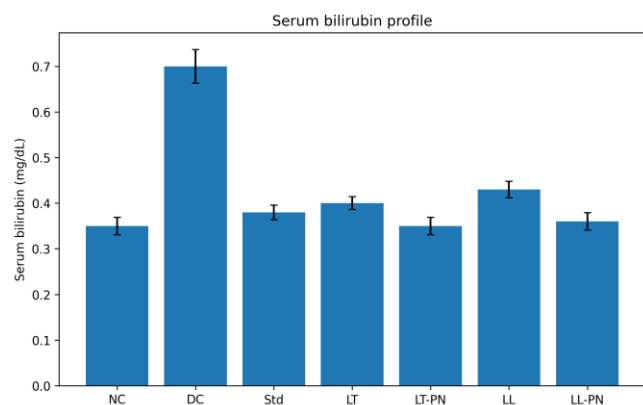


Figure 3. Serum bilirubin profile in the experimental groups. Values are mean $\pm$ SD, $n = 6$, from the present work dataset.

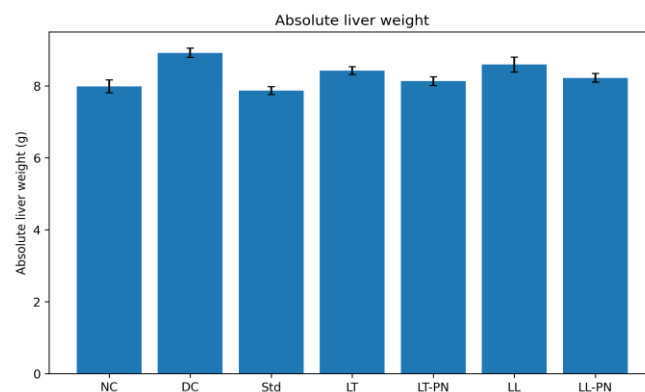


Figure 4. Absolute liver weight in the experimental groups. Values are mean $\pm$ SD, $n = 6$, as reported in the present work.

Absolute liver weight

Absolute liver weight increased from 7.982 ± 0.18 g in the normal-control group to 8.914 ± 0.13 g in the disease-control group. Treatment groups showed lower values: 7.867 ± 0.11 g for the standard, 8.421 ± 0.11 g for L-theanine, 8.127 ± 0.12 g for LT-SE-PN4, 8.587 ± 0.21 g for L-leucine and 8.217 ± 0.12 g for LL-SE-PN4. The nanoparticle-treated groups were therefore closer to the normal-control value than the corresponding free-bioactive groups.

Histopathological findings

The original present work histopathology composite is shown in Figure 5. Normal-control liver tissue showed preserved hepatic architecture. The disease-control tissue displayed focal perivascular leukocytic infiltration, mild hepatocellular necrosis, pyknotic nuclei, condensed cytoplasm and marked cytoplasmic vacuolation. The standard-treated section showed no lesion of pathological significance. The present work reported normal histology for the nanoparticle-treated groups.

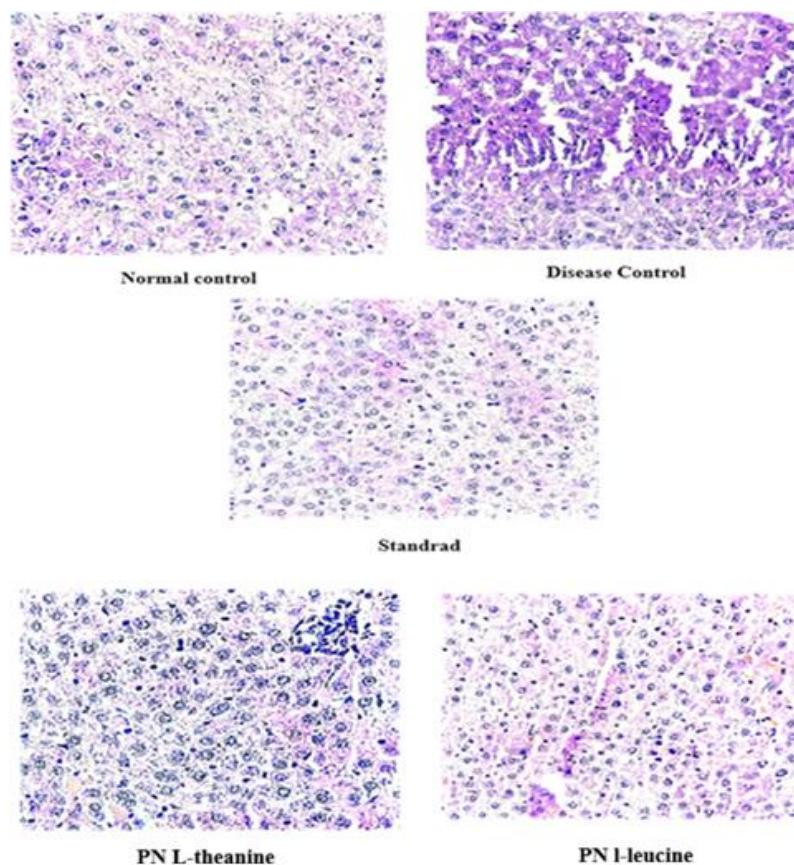


Figure 5. Original histopathological comparison of liver sections reproduced from the present work. The source composite contains panels for normal control, disease control, standard, PN L-theanine and PN L-leucine. H&E-stained liver sections; magnification/scale information is retained as in the source figure.

CONCLUSION:

The present study demonstrated that optimized L-theanine-loaded (LT-SE-PN4) and L-leucine-loaded (LL-SE-PN4) polymeric nanoparticles produced measurable systemic exposure following oral administration and were associated with improved hepatic biochemical and histopathological outcomes in a paracetamol-induced hepatic injury model. LL-SE-PN4 exhibited an earlier T_{max} (2 h) and higher reported AUC_{0-24} than LT-SE-PN4, indicating formulation-dependent differences in systemic exposure. Both formulations showed substantially improved relative bioavailability compared with the reference condition.

In the hepatoprotective assessment, nanoparticle treatment reduced the elevated AST, ALT, ALP and bilirubin levels observed in disease-control animals, with values approaching those of normal controls. Both formulations also produced liver-weight profiles closer

to normal animals, while histopathological findings indicated better preservation of hepatic architecture compared with the disease-control group. The nanoparticle characteristics, including approximately 125–130 nm particle size, high entrapment efficiency and sustained release, provide a plausible formulation basis for the observed pharmacokinetic behavior.

Overall, the findings support the potential of polymeric nanoparticle delivery to enhance oral exposure of L-theanine and L-leucine while producing favorable hepatic outcomes in this experimental model. However, a direct causal relationship between increased systemic exposure and hepatoprotection cannot be established from the present data. Further studies incorporating oxidative-stress, inflammatory, molecular, tissue-distribution and comprehensive toxicological assessments are warranted to confirm the underlying mechanisms and therapeutic potential.

Table 1. Pharmacokinetic parameters of optimized polymeric nanoparticles

Parameter	LT-SE-PN4	LL-SE-PN4
C1 ($\mu\text{g/mL}$)	0.37 ± 0.02	1.00 ± 0.03
AUC_{0-24} ($\mu\text{g/mL}\cdot\text{h}$)	22.36 ± 2.21	41.56 ± 2.78
C_{max} ($\mu\text{g/mL}$)	1.54 ± 0.42	2.98 ± 0.74
T_{max} (h)	4 ± 0.08	2 ± 0.06
Relative bioavailability (%)	319.92	320.91

Table 2. Optimized formulation characteristics

Parameter	LT-SE-PN4	LL-SE-PN4
Particle size (nm)	127.21 ± 1.11	126.11 ± 1.09
Zeta potential (mV)	-24.21 ± 1.09	-24.81 ± 1.19
Entrapment efficiency (%)	85.17 ± 0.30	81.37 ± 0.80
Morphology	Spherical	Spherical

Table 3. Effect on serum hepatic biochemical markers

Group	AST (IU/L)	ALT (IU/L)	ALP (IU/L)
Normal control	110.16 ± 5.38	60.89 ± 2.26	235.76 ± 8.97
Disease control	205.34 ± 7.04	123.64 ± 3.36	405.62 ± 7.65
Standard	112.13 ± 6.19	66.92 ± 3.65	270.02 ± 10.79
L-theanine	120.96 ± 9.23	69.34 ± 3.27	295.71 ± 10.85
LT-SE-PN4	111.16 ± 7.78	61.96 ± 2.78	279.48 ± 10.83
L-leucine	148.60 ± 4.85	68.44 ± 3.98	284.53 ± 13.12
LL-SE-PN4	113.16 ± 7.78	62.96 ± 2.78	274.48 ± 10.83

Table 4. Serum bilirubin and absolute liver weight

Group	Bilirubin (mg/dL)	Liver weight (g)
Normal control	0.350 ± 0.019	7.982 ± 0.18
Disease control	0.700 ± 0.037	8.914 ± 0.13
Standard	0.380 ± 0.016	7.867 ± 0.11
L-theanine	0.400 ± 0.014	8.421 ± 0.11
LT-SE-PN4	0.350 ± 0.019	8.127 ± 0.12
L-leucine	0.430 ± 0.018	8.587 ± 0.21
LL-SE-PN4	0.360 ± 0.019	8.217 ± 0.12

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Conflicts of interest: There is no conflict of interest

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