NLC for Intranasal Delivery in Alzheimer's disease- Pharmacokinetic, Biodistribution and PD study

Presented by:

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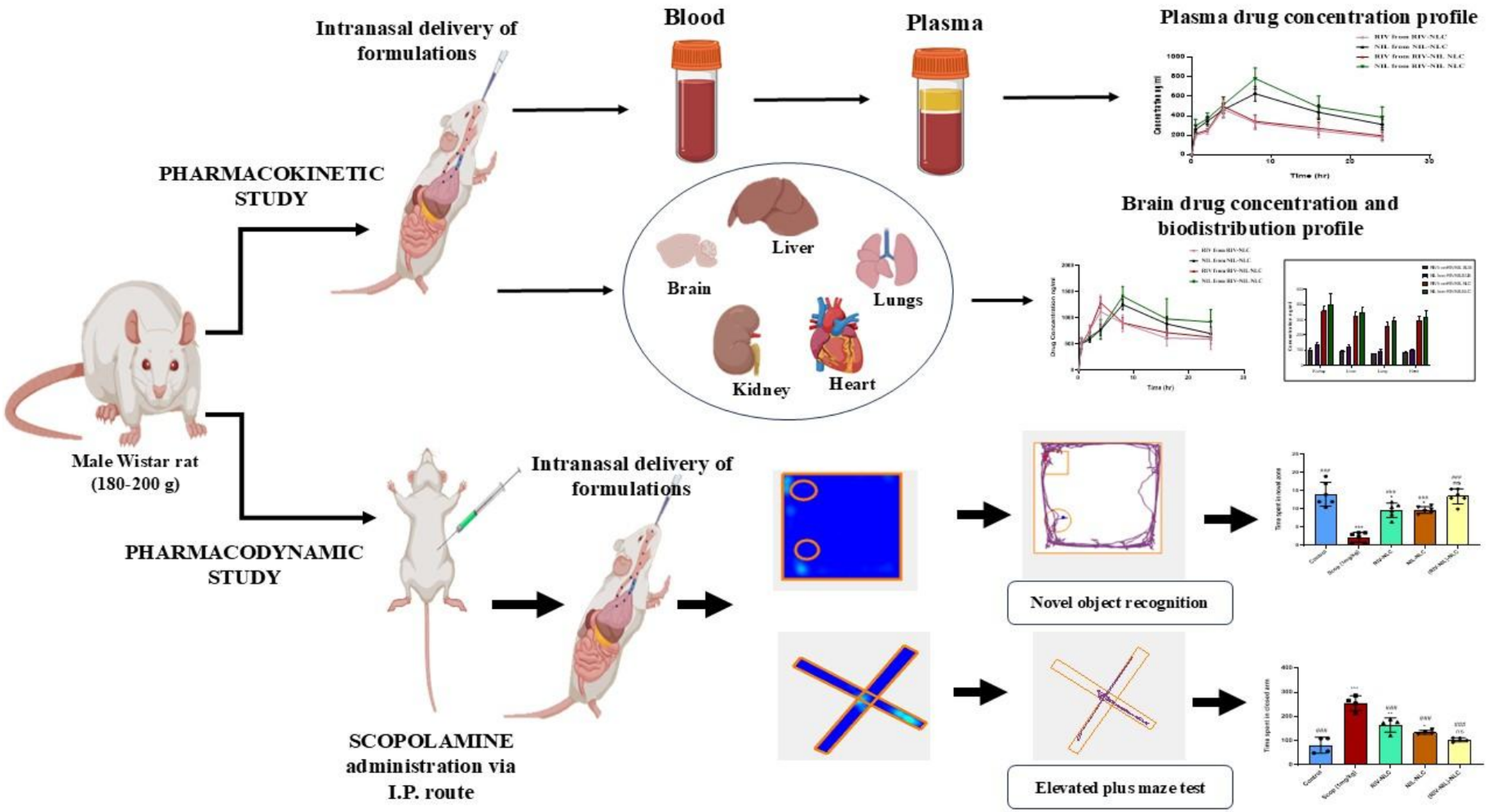
NEXT-GENERATION DELIVERY INNOVATIONS

OVERVIEW


Intranasal delivery of formulations
Blood
Plasma
Plasma drug concentration profile
PHARMACOKINETIC STUDY
Liver
Brain
Lungs
Kidney
Heart
Brain drug concentration and biodistribution profile
Male Wistar rat (180-200 g)
PHARMACODYNAMIC STUDY
Intranasal delivery of formulations
SCOPOLAMINE administration via I.P. route
Novel object recognition
Elevated plus maze test

ABSTRACT

Introduction: Alzheimer's disease (AD) is complex neurodegenerative disorder that remains challenging to treat with monotherapy. This complexity underscores the need for combination therapies, which offer a more effective treatment strategy. In this study, a dual approach was explored by combining an acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzyme inhibitor (RV) with a kinase inhibitor (KI) for managing AD. This innovative combination targets multiple pathways involved in AD progression, potentially improving therapeutic outcomes and addressing the limitations of single-drug treatments.

Methods: This study aimed to enhance the brain bioavailability of RV and KI using intranasal delivery via nanostructured lipid carriers (NLCs). NLCs were prepared using a modified emulsification method and evaluated for reversing scopolamine-induced AD-associated symptoms (AD) in male Wistar rats. Scopolamine (1mg/kg, intraperitoneal) was administered to induce AD-like symptoms as a negative control. AD-affected rats received intranasal treatment with individual and combination drug suspensions and NLCs. Pharmacokinetic, biodistribution, and pharmacodynamic studies, including Novel Object Recognition (NOR) and Elevated Plus Maze (EPM) tests, were conducted. The results were statistically analyzed, comparing the effects of NLCs with drug suspensions.

Results: The pharmacokinetic (PK) study revealed that NLC-loaded formulations of RV and KI achieved significantly higher Cmax values compared to suspensions. RV showed 1122.7 ± 309.6 ng/ml at 4h, and KI achieved 1257.2 ± 101.0 ng/ml at 8h, showing a 3.5–4.1-fold increase. The (RV-KI) NLC exhibited the highest brain concentrations, with RV at 1292.9 ± 111.0 ng/ml (4h) and KI at 1414.9 ± 186.3 ng/ml (8h), demonstrating a 5–5.9-fold increase via the intranasal route versus suspensions. Plasma concentrations of RV (596.6 ± 106.9 ng/ml at 4h) and KI (782.8 ± 108.8 ng/ml at 8h) were 2.5–3.3-fold higher, confirming controlled, sustained release. Biodistribution showed the highest drug levels in the kidney and the lowest in the heart. Behavioral tests supported therapeutic efficacy, with (RV-KI) NLC restoring memory in scopolamine-treated rats in the NOR test (**$p < 0.001$) and reducing anxiety in the EPM test, aligning with normal behavior and outperforming RV-NLC and KI-NLC.

Conclusion: The (RV-KI) NLC formulation significantly improved brain drug delivery through intranasal route, with sustained release resulting in higher drug concentrations in both brain and plasma. Behavioral studies demonstrated its efficacy in reversing scopolamine-induced memory and anxiety deficits, as evidenced by improved NOR and EPM test outcomes, highlighting its potential for Alzheimer's treatment.

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References: [1] Anwar et al., IJBM. 2024; [2] Kaushik et al., Eneuro. 2023, [3] Akram et al.,KJMS. 2023, [4] Qamar et al., IJP. 2021, [5] Yadang et al., IJAD. 2020

Drug concentration in Plasma after intranasal administration of suspension

Table 1: Plasma drug concentration after intranasal delivery of the suspension for the targeted delivery

	RIV from RIV-SUS		NIL from NIL-SUS		RIV from (RIV-NIL) SUS		NIL from (RIV-NIL) SUS	
Time (hr)	**Conc. (ng/ml)**	**SD**	**Conc. (ng/ml)**	**SD**	**Conc. (ng/ml)**	**SD**	**Conc. (ng/ml)**	**SD**
0	0	0	0	0	0	0	0	0
0.5	113.29	12.46	155.82	16.78	126.65	11.03	131.75	21.66
2	**180.92**	**27.62**	171.16	19.48	**196.22**	**23.52**	150.95	12.04
4	159.01	5.57	**218.02**	**21.10**	138.52	16.91	**231.16**	**30.89**
8	114.63	8.52	145.90	18.93	125.02	13.75	185.60	21.45
16	101.72	11.41	113.74	12.01	87.76	8.58	145.50	17.54
24	45.58	5.80	63.19	9.52	35.48	2.20	71.39	3.75

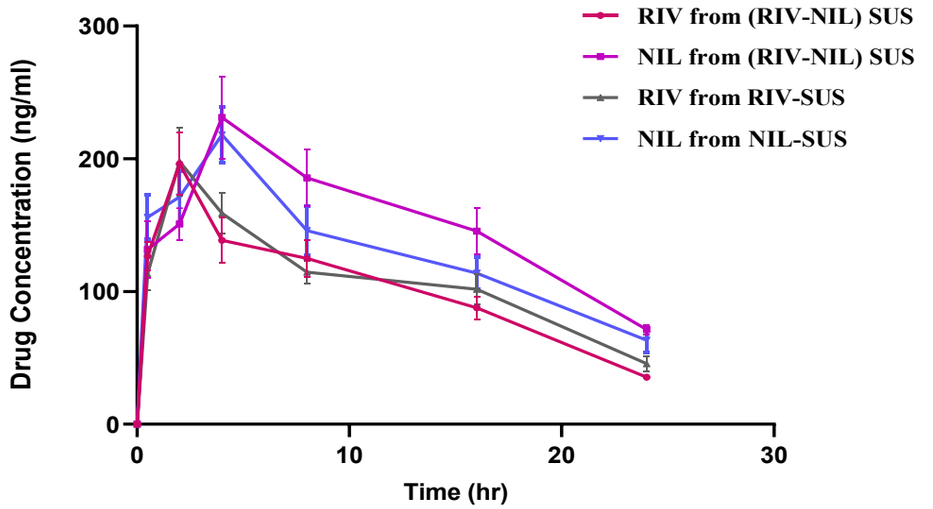


Figure 1: Illustrates the plasma drug concentration profile of RIV and NIL after intranasal administration of suspensions and the data are expressed as mean ±SD (n = 3).

Inferences:

RIV, being relatively lipophilic, can be absorbed through the nasal mucosa via transcellular and paracellular pathways. As, IN administration bypasses first-pass metabolism, leading to quicker onset and potentially higher bioavailability compared to oral administration.

•NIL, is a tyrosine kinase inhibitor with high lipophilicity and relatively poor water solubility. Since, NIL is P-gp inhibitor therefore, inhibition of P-gp by NIL can enhance drug delivery to protected areas like the BBB, where P-gp usually acts as a barrier.

•But on comparison amongst RIV-SUS, NIL-SUS, and (RIV-NIL) SUS, it can be observed that RIV and NIL concentration is found to be higher in the plasma suggesting that the co-administration might alter absorption dynamics due to interactions at the nasal mucosa. Competitive absorption at mucosal surfaces slightly reduced individual drug uptake. One drug being P-gp inhibitor i.e., NIL positively influenced the concentration of RIV in the plasma thereby, collectively augmenting the concentration of both the drugs.

Drug concentrations in the Brain after intranasal administration of suspension

Table 2: Brain drug concentration after intranasal delivery of the suspension for the targeted delivery

Time (h)	RIV from RIV-SUS		NIL from NIL-SUS		RIV from (RIV-NIL) SUS		NIL from (RIV-NIL) SUS	
	Conc. (ng/ml)	SD	Conc. (ng/ml)	SD	Conc. (ng/ml)	SD	Conc. (ng/ml)	SD
0	0	0	0	0	0	0	0	0
0.5	180.50	14.33	215.06	14.77	180.50	3.76	181.68	13.45
2	218.57	21.44	254.99	18.81	282.41	36.25	310.11	27.40
4	156.86	18.84	306.43	28.41	182.82	13.51	394.42	31.26
8	135.14	11.58	211.59	22.57	145.36	57.27	265.67	19.02
16	123.92	12.43	160.77	16.76	107.64	19.14	194.90	12.90
24	63.45	8.50	111.36	9.37	60.90	6.39	118.78	14.52

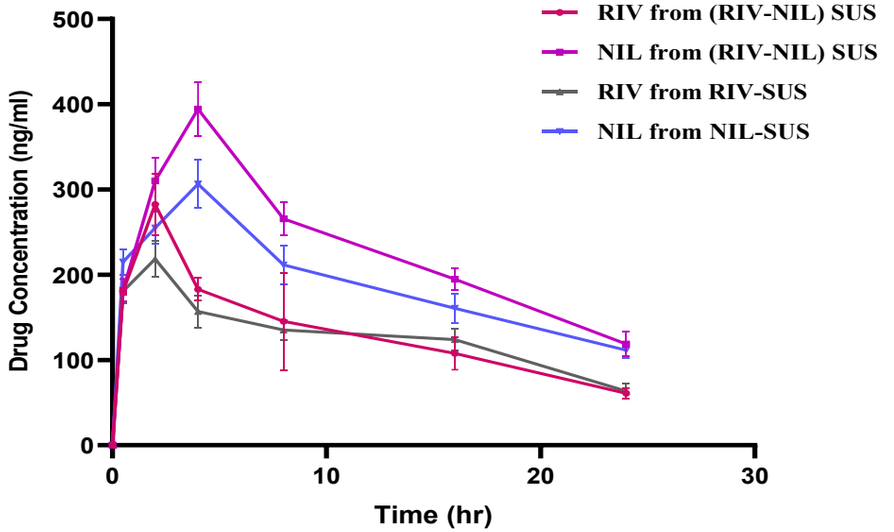


Figure 2: Illustrates the brain drug concentration profile of RIV and NIL after intranasal administration of suspensions and the data are expressed as mean ±SD (n = 3).

Inferences:

- It can be observed from the data obtained that (RIV-NLC) SUS showed higher drug concentrations of RIV and NIL in the brain at 2 and 4hr. RIV, a cholinesterase inhibitor, and NIL, a tyrosine kinase inhibitor, may interact synergistically to enhance the permeability.
- NIL can inhibit certain efflux transporters in the brain and nasal mucosa, such as P-glycoprotein (P-gp), which are known to limit the entry of many drugs, into the brain.
- By inhibiting P-gp, NIL could reduce the active efflux of RIV and potentially even itself, thus enhancing brain penetration. RIV itself may also contribute to altered brain permeability, and increased permeability transiently.
- But the concentration of the drugs in the brain could be increased by incorporating these drugs in NLC either induvial or in combination. As it can be observed that both drug concentration was higher in brain when administered via IN route.

Drug concentrations in Plasma after intranasal administration of NLCs

Table 3: Plasma drug concentration after intranasal delivery of the NLCs for the targeted delivery

Time (hr)\	RIV from RIV-NLC	NIL from NIL-NLC	RIV from (RIV-NIL) NLC	NIL from (RIV-NIL) NLC
	Conc. (ng/ml) ± SD	Conc. (ng/ml) ± SD	Conc. (ng/ml) ± SD	Conc. (ng/ml) ± SD
0	0	0	0	0
0.5	197.2 ± 19.4	256.7 ± 42.1	214.9 ± 12.6	296.4 ± 68.0
2	237.1 ± 24.1	346.0 ± 48.3	251.9 ± 16.3	372.2 ± 57.0
4	465.9 ± 90.0	463.2 ± 75.8	596.6 ± 106.9	513.5 ± 80.4
8	327.4 ± 72.0	626.6 ± 75.5	342.3 ± 67.2	782.8 ± 108.8
16	245.9 ± 67.9	435.8 ± 76.1	269.7 ± 65.1	515.2 ± 68.3
24	167.4 ± 37.6	310.8 ± 55.4	194.2 ± 42.7	453.7 ± 83.8

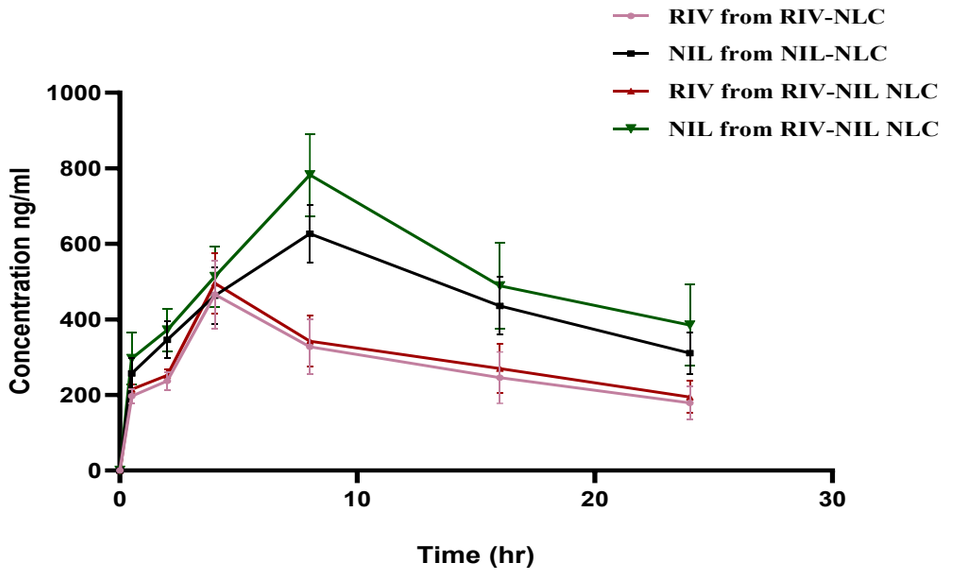


Figure 3: Illustrates the plasma drug concentration profile of RIV and NIL after intranasal administration of NLCs and the data are expressed as mean ±SD (n = 3).

Inferences:

- ❑ It can be observed from the data obtained that the concentration of RIV was found to be highest at 4hr indicating rapid absorption due to its lipophilic nature and small molecular size. Whereas, NIL showed higher concentration at 8hr reflecting controlled and prolonged release properties of NLCs.
- ❑ There was 2.5 to 3.3-fold increase in the concentration of RIV and NIL in the plasma when administered using NLC via IN route than the SUS. The superior performance of NLCs in delivering RIV and NIL intranasally highlights their ability to enhance absorption, bypass first-pass metabolism, and sustain drug levels, making them an efficient delivery system compared to conventional suspensions.

Drug concentration in the Brain after intranasal administration of NLCs

Table 4: Brain drug concentration after intranasal delivery of the NLCs for the targeted delivery

Time (hr)	RIV from RIV-NLC	NIL from NIL-NLC	RIV from (RIV-NIL) NLC	NIL from (RIV-NIL) NLC
	Conc. (ng/ml) ± SD	Conc. (ng/ml) ± SD	Conc. (ng/ml)	Conc. (ng/ml)
0	0	0	0	0
0.5	493.6 ± 127.3	506.5 ± 99.0	493.6 ± 127.3	518.9 ± 105.7
2	761.0 ± 103.0	591.3 ± 60.6	761.0 ± 103.0	636.6 ± 88.7
4	1122.7 ± 309.6	774.0 ± 105.1	1292.9 ± 111.0	782.2 ± 189.1
8	899.9 ± 160.7	1257.2 ± 101.0	908.4 ± 101.7	1414.9 ± 186.3
16	617.3 ± 144.4	887.8 ± 138.6	719.5 ± 57.4	982.4 ± 384.6
24	596.9 ± 202.7	701.7 ± 127.6	635.5 ± 133.8	923.9 ± 240.1

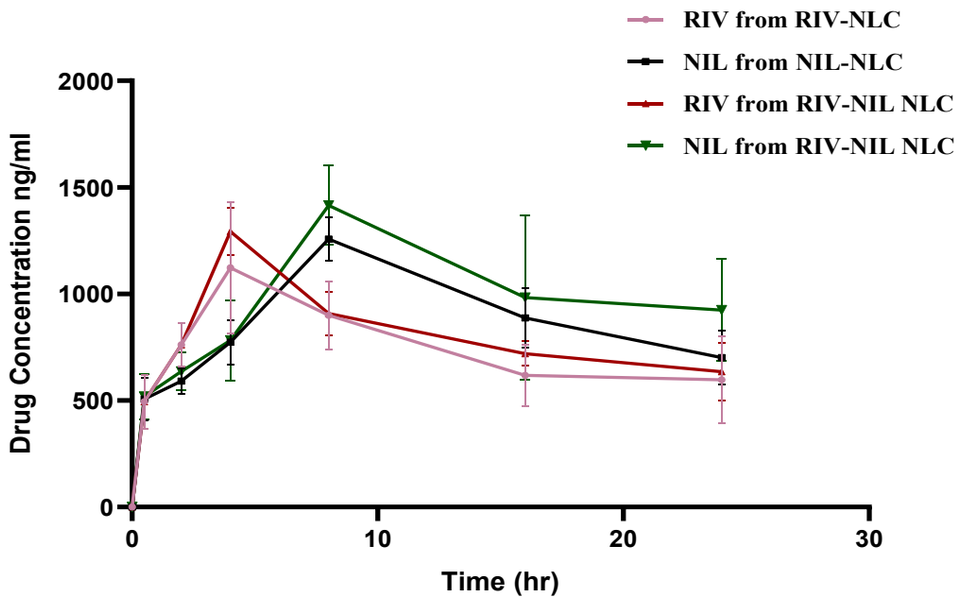


Figure 4: Illustrates the plasma drug concentration profile of RIV and NIL after intranasal administration of NLCs and the data are expressed as mean ±SD (n = 3)

Inferences:

- ❑ It can be observed from the data obtained that the concentration of RIV was found to be highest at 4hr indicating rapid absorption and brain delivery due to RIV favorable lipophilicity and small molecular size, supported by NLC encapsulation. Whereas, NIL showed higher concentration at 8hr Controlled and sustained release from the NLC formulation allows prolonged brain uptake.
- ❑ There was 3.5 to 4.10-fold increase in the concentration of RIV and NIL in the brain when administered using NLC loaded with these drug induvial. But, (RIV-NIL) NLC showed 4.56 to 5.15-fold increase in the concentration of RIV and NIL in the brain via IN route than the combination loaded SUS.
- ❑ The significant increase in brain concentration of RIV and NIL using NLCs via the intranasal route results from enhanced solubility, stability, permeability, prolonged nasal retention, and direct brain delivery. These properties make NLCs a superior drug delivery system for targeting the brain, overcoming the limitations of traditional suspensions.

Estimation of Pharmacokinetic Parameters in Plasma after intranasal administration of suspensions and NLCs

Parameters	FORMULATIONS							
	RIV SUS	NIL SUS	RIV-NIL SUS		RIV NLC	NIL NLC	RIV-NIL NLC	
			RIV	NIL			RIV	NIL
T_{max} (hr)	2	4	2	4	4	8	4	8
C_{max}(ng/ml)	197.92 ± 32.73	218.02 ± 76.24	196.22 ± 23.74	231.16 ± 61.62	465.89 ± 98.81	626.59 ± 72.04	596.56 ± 85.23†	782.75 ± 53.12†
$AUC_{0\rightarrow t}$ (ng.hr/ml)	2648.97 ± 172.82	3186.56 ± 178.32	2511.39 ± 214.82	3678.46 ± 888.12	6660.18 ± 416.12	10804.95 ± 589.62	7486.89 ±310.82†	13195.18 ± 451.55†
$AUC_{0\rightarrow \infty}$ (ng.hr/ml)	3414.15 ± 209.81	4285.93 ± 281.12	3022.24 ± 362.13	4953.79 ± 747.01	10655.34 ± 312.01	17896.36 ± 657.82	12970.21 ± 901.12†	26506.48 ± 357.77†
$t_{1/2}$	11.63 ± 4.07	12.05 ± 5.28	11.09 ± 3.64	12.37 ± 8.32	16.53 ± 9.64	15.81 ± 7.32	19.57 ± 9.75	20.62 ± 7.28

Inference:

The C_{max}(ng/ml) of RIV and NIL from NLC was 2.2 to 2.6-fold higher than that from SUS in the plasma signifying the significant ($p<0.05$) increase in the concentration of RIV and NIL in the plasma. NLC was found to have a greater area under the curve (AUC) than SUS of the drugs and their combination. Therefore, developing NLC resulted in a roughly 4-fold increase in bioavailability.

Pharmacokinetic Parameters of RIV and NIL in Wistar Rats in Brain after intranasal administration of the RIV-NIL-SUS and RIV-NIL-NLC.

Parameters	Formulations							
	RIV SUS	NIL SUS	RIV-NIL SUS		RIV NLC	NIL NLC	RIV-NIL NLC	
			RIV	NIL			RIV	NIL
T_{max} (h)	2	4	2	4	4	8	4	8
C_{max}(ng/ml)	218.57 ± 56.23	306.43 ± 77.12	256.88 ± 46.72	394.42 ± 87.01	1122.70 ± 88.02	1257.176 ± 223.73	1292.94 ± 293.37†	1414.87 ± 512.81†
$AUC_{0\rightarrow t}$ (ng.hr/ml)	3134.84 ± 271.90	4574.68 ± 212.56	3054.99 ± 213.93	5521.85 ± 357.63	18042.45 ± 412.72	21315.42 ± 781.21	19452.17 ± 618.13†	24153.02 ± 541.83†
$AUC_{0\rightarrow \infty}$ (ng.hr/ml)	4482.26 ± 143.81	6342.53 ± 301.34	4620.93 ± 246.84	7176.78 ± 801.12	36488.79 ± 461.12	40566.43 ± 448.82	47906.35 ± 996.33†	58835.58 ± 863.99†
$t_{1/2}$	14.71 ± 3.45	12.74 ± 2.31	15.54 ± 3.94	11.04 ± 5.01	21.41 ± 5.91	19.01 ± 7.01	31.04 ± 11.12	26.02 ± 12.91

Inference:

The groups receiving NLC had higher drug concentrations in the brain at each time point than the groups receiving drug suspension, according to the observations. There was a significant difference *($p < 0.05$)* in the brain concentration between the two groups. The concentration in the brain is as follows RIV-NIL-NLC> NIL-NLC> RIV-NLC> RIV-NIL SUS> NIL-SUS> RIV-SUS as depicted in the table. when RIV-NIL-NLC was given intranasally instead of RIV-NIL SUS, the concentrations of RIV and NIL in the brain increased by 5-fold and 3.5-fold, respectively.

Comparison of the Drug Concentration Profile in Different Organs after intranasal administration of the suspensions and NLCs

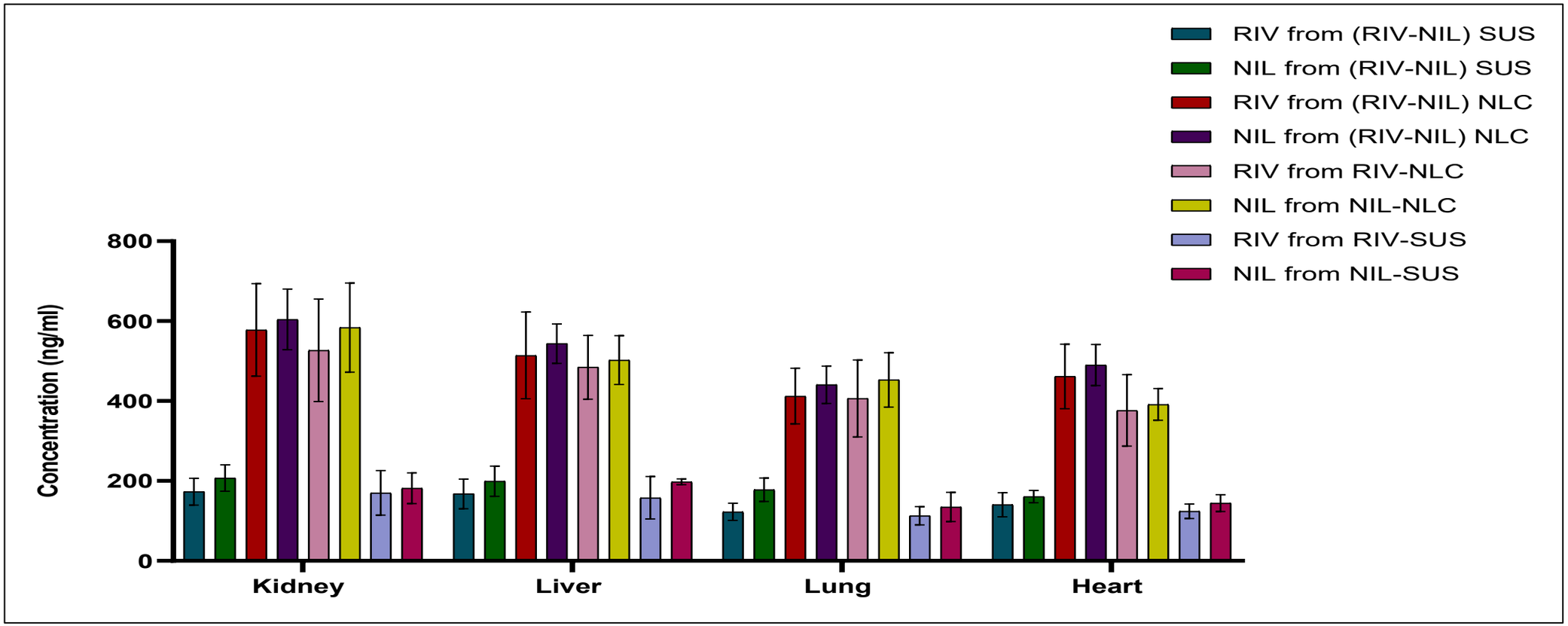
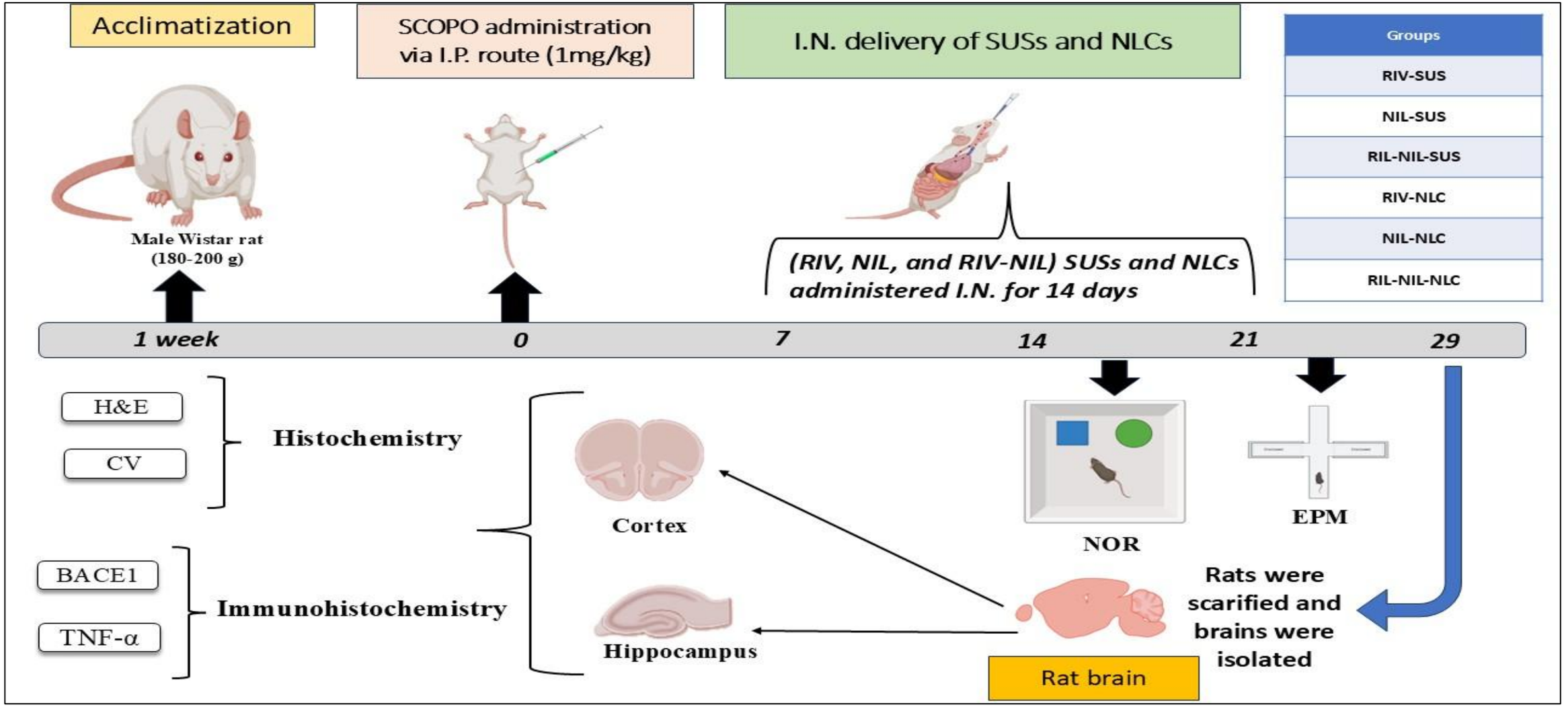


Figure 5: Illustrates the drug concentration profile of RIV and NIL in different organs after intranasal administration of RIV-SUS, NIL-SUS, RIV-NIL SUS, RIV-NLC, NIL-NLC, and RIV-NIL NLC in the rats. ****** p< 0.001, ** p< 0.01, * p< 0.05= Statistically significant compared to SUS.***

Grouping of Animals for Pharmacodynamics Study

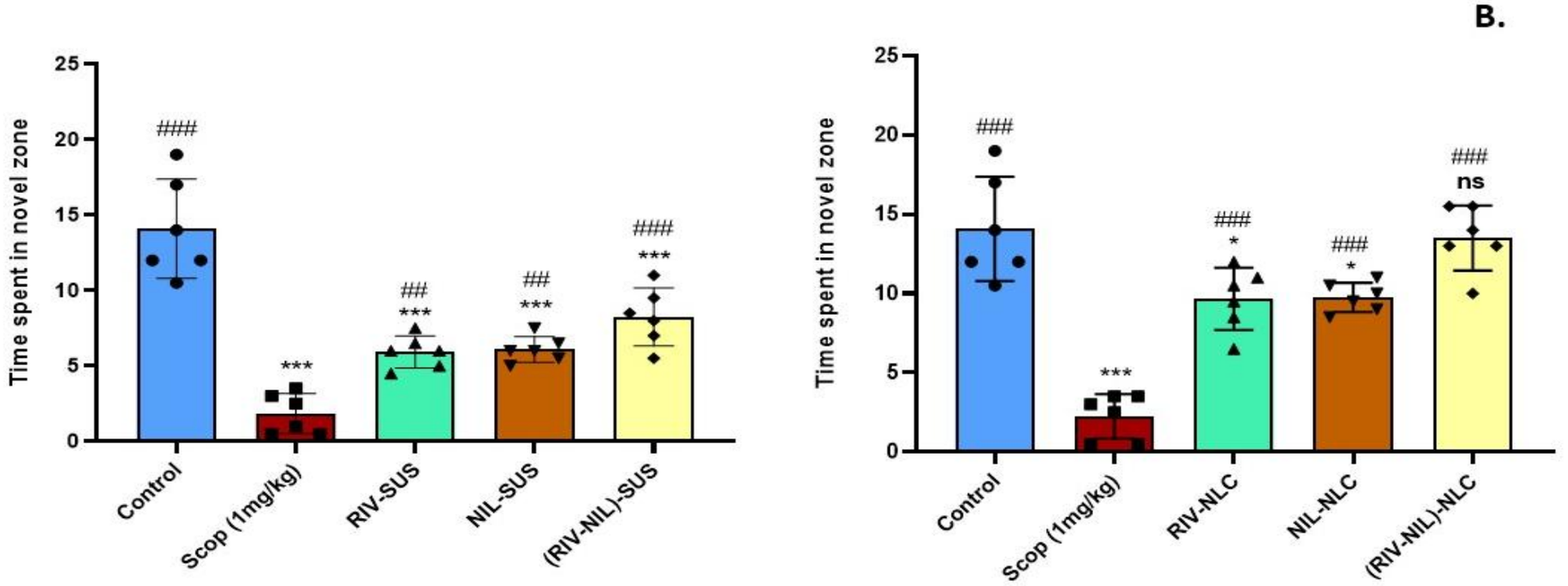
Groups	No. of Rats	Treatments	Route
1	6	Positive control (No Alzheimer's Disease)	-
2	6	Negative control (Induced Alzheimer's Disease) - SCOPO	I.P.
3	6	RIV-SUS	I.N.
4	6	NIL-SUS	I.N.
5	6	RIL-NIL-SUS	I.N.
6	6	RIV-NLC	I.N.
7	6	NIL-NLC	I.N.
8	6	RIL-NIL-NLC	I.N.

Pictorial Representation of the Studies Carried Out



Cognitive Neuroscience Investigation

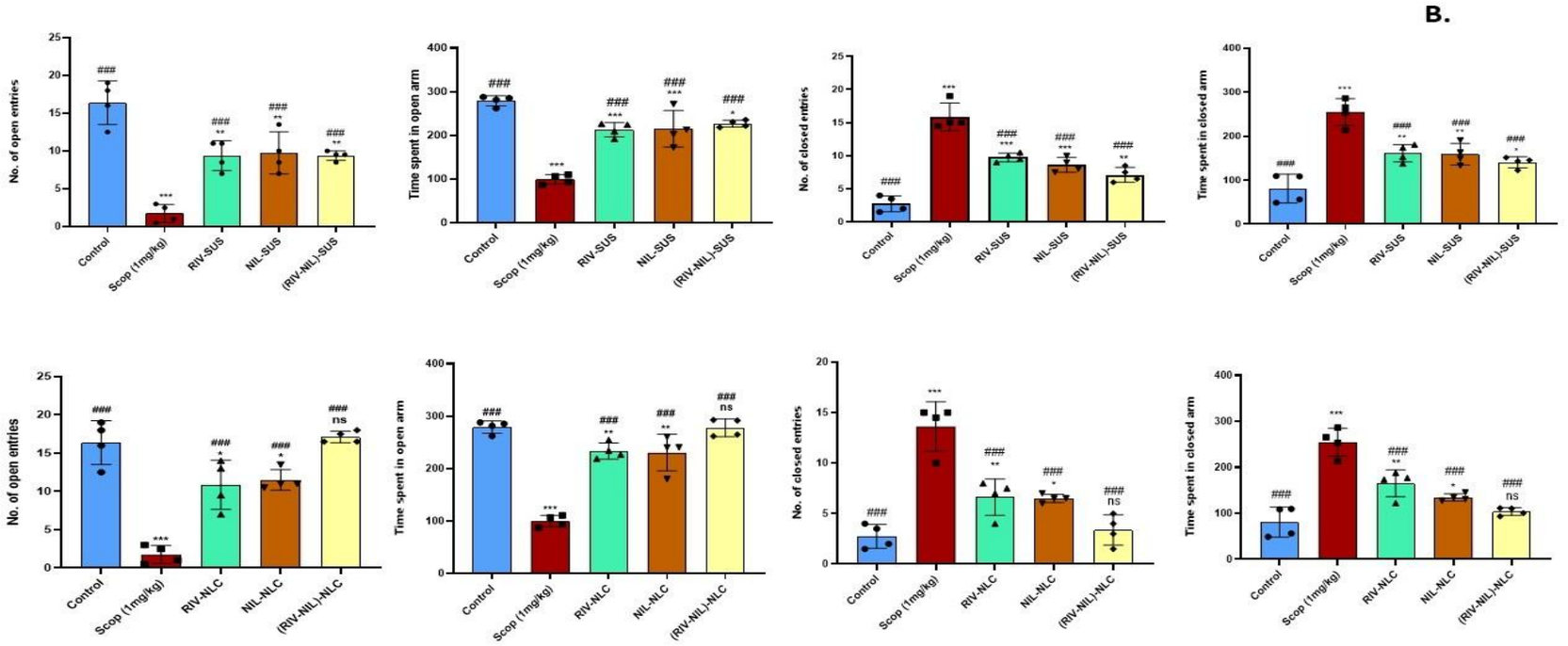
Novel Object Recognition (NOR)



- Statistical analysis confirmed that the **SCOPO-treated group exhibited a drastic reduction in time spent in the novel zone compared to the control group *(***p < 0.001),* indicating severe AD-like symptoms**.
- Treatment with RIV-SUS and NIL-SUS independently resulted in significant cognitive improvement *(**p < 0.01)*, suggesting a partial reversal of cognitive deficits, with the **combination treatment (RIV-NIL-SUS) demonstrating the highest restoration of cognitive function *(***p<0.001, vs. SCOPO; ##p<0.01, or ###p<0.001*, vs. individual treatments), implying a potential synergistic effect.**

Cognitive Neuroscience Investigation

Elevated Plus Maze (EPM)



- Treatment with **RIV-SUS, NIL-SUS, and RIV-NIL-SUS effectively reversed SCOP-induced anxiety**, as evidenced by a significant increase in open-arm entries and time spent in the open-arm *(*p < 0.05, p < 0.01, or p < 0.001 vs. SCOP).*
- Treatment with **RIV-NLC, NIL-NLC, and RIV-NIL NLC improved open-arm exploration, suggesting potential anxiolytic effects.**
- According to statistical analysis, **RIV-NLC, NIL-NLC, and RIV-NIL NLC treatments** dramatically reversed the behaviour of SCOPO, which considerably hindered open-arm exploration **(p<0.001 compared to control)** ***(p<0.05 to p<0.001).***

Histopathological Studies

Hematoxylin and Eosin (H &E) Staining

Hippocampus

- There is **no evidence of any cellular damage in the positive control group** in terms of **cellular disintegration, hemorrhage, vacuolation, or pyknosis.**
- The negative control group has marked cellular disintegration and pyknosis caused by SCOPO, which signifies hippocampal neurotoxicity.
- When **RIV, NIL, and RIV-NIL-SUS**, as well as **RIV, NIL, and RIV-NIL-NLC**, were compared with the negative control group, RIV suspension showed only minimal improvement against histopathological damage caused by SCOPO. NIL suspension and RIV-NIL suspension showed moderate improvement, but upon comparing these two groups, the **RIV-NIL-SUS treated group exhibited superior improvement**.
- When **RIV-NLC, NIL-NLC, and RIV-NIL-NLC treated group were evaluated for neuroprotective effect** against a negative control group, it was found that all the **three NLC-treated groups showed superior effects than all three SUS groups**

Cortex

- There is **no evidence of any cellular damage in the positive control group** in terms of **cellular disintegration, hemorrhage, vacuolation, or pyknosis.**
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- When **RIV-NLC, NIL-NLC, and RIV-NIL-NLC treated group were evaluated for neuroprotective effect** against a negative control group, it was found that all the **three NLC-treated groups showed superior effects than all three SUS groups**

Cresyl Violet (CV) Staining

Hippocampus

- There is **no evidence of any cellular damage in the positive control group** in terms of **cellular disintegration, hemorrhage, vacuolation, or pyknosis.**
- The negative control group has marked cellular disintegration and pyknosis caused by SCOPO, which signifies hippocampal neurotoxicity.
- When **RIV, NIL, and RIV-NIL-SUS**, as well as **RIV, NIL, and RIV-NIL-NLC**, were compared with the negative control group, RIV suspension showed only minimal improvement against histopathological damage caused by SCOPO. NIL suspension and RIV-NIL suspension showed moderate improvement, but upon comparing these two groups, the **RIV-NIL-SUS treated group exhibited superior improvement**.
- When **RIV-NLC, NIL-NLC, and RIV-NIL-NLC treated group were evaluated for neuroprotective effect** against a negative control group, it was found that all the **three NLC-treated groups showed superior effects than all three SUS groups,** except for RIV-NLC, which showed better outcome for RIV-SUS and NIL-SUS but almost comparable effect to RIV-NIL-NLC

Cortex

- There is **no evidence of any cellular damage in the positive control group** in terms of **cellular disintegration, hemorrhage, vacuolation, or pyknosis.**
- The negative control group has marked cellular disintegration and pyknosis caused by SCOPO, which signifies hippocampal neurotoxicity.
- When **RIV-SUS, NIL-SUS, and RIV-NIL-SUS**, as well as **RIV-NLC, NIL-NLC, and RIV-NIL-NLC**, were compared with the negative control group, RIV suspension showed only minimal improvement against histopathological damage caused by SCOPO. NIL suspension and RIV-NIL suspension showed moderate improvement, but upon comparing these two groups, the **RIV-NIL-SUS treated group exhibited superior improvement**.
- When **RIV-NLC, NIL-NLC, and RIV-NIL-NLC treated group were evaluated for neuroprotective effect** against a negative control group, it was found that all the **three NLC-treated groups showed superior effects than all three SUS groups.** Further, when RIV, NIL, and RIV-NIL-NLC were evaluated against each other, it was found that RIV-NIL-NLC was most effective, followed by NIL-NLC and RIV-NLC. In conclusion, all 3 NLC-treated groups were most effective, followed by RIV-NIL-SUS, NIL-SUS, and RIV-SUS.

Immunohistochemistry

Beta-site amyloid precursor protein cleaving enzyme (BACE1)

Hippocampus

- There is a strong negative expression of BACE1 in the positive control group, whereas in the negative control group, the expression is strong and positive.
- When the expression pattern of various treatment groups was compared to the negative control group, RIV-SUS showed moderately strong expression, whereas NIL–SUS, and RIV–NIL–SUS showed mild to moderate expression.
- Upon comparing the expression patterns between the three SUS groups, strong expression was seen in RIV–SUS followed by NIL–SUS and RIV–NIL`– SUS. RIV – NLC showed mild BACE1 expression, followed by NIL – NLC, and RIV – NIL – NLC showed minimal expression.

Cortex

- There is a strong negative expression of BACE1 in the positive control group, whereas in the negative control group, the expression is strong and positive.
- When the expression pattern of various treatment groups was compared to the negative control group, RIV -SUS showed strong negative expression, which is almost comparable to that of the negative control group. NIL–SUS and RIV–NIL–SUS showed moderate expression.
- Upon comparing the expression patterns between the three SUS groups, strong positive expression was seen in RIV – SUS followed by NIL–SUS, and RIV–NIL–SUS. RIV–NLC showed mild to moderate positive BACE1 expression, whereas NIL-NLC showed mild expression, and RIV–NIL–NLC showed minimal positive expression.

Tumor Necrosis Factor - alpha (TNF - α)

Hippocampus

- There is a strong negative expression of TNF-α in the positive control group, whereas in the negative control group, the expression is strong and positive.
- When the expression pattern of various treatment groups was compared to the negative control group, RIV - SUS showed strong to moderately strong positive expression, whereas NIL–SUS and RIV–NIL–SUS showed moderate positive expression.
- Upon comparing the expression patterns between the three SUS groups, strong expression was seen in RIV – SUS followed by NIL–SUS, and RIV–NIL–SUS. RIV–NLC showed mild TNF-α expression, followed by NIL–NLC, and RIV–NIL–NLC showed minimal expression.

Cortex

- There is a strong negative expression of TNF-α in the positive control group, whereas in the negative control group, the expression is strong and positive.
- When the expression pattern of various treatment groups was compared to the negative control group, RIV-SUS showed strong negative expression, which is almost comparable to that of the negative control group. NIL–SUS and RIV-NIL–SUS showed moderate expression
- Upon comparing the expression patterns between the three SUS groups, strong positive expression was seen in RIV–SUS followed by NIL–SUS, and RIV–NIL–SUS. RIV–NLC showed mild to moderate positive TNF-α expression, whereas NIL–NLC showed mild expression, and RIV–NIL–NLC showed minimal positive expression.

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NEXT-GENERATION
DELIVERY INNOVATIONS