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Hepatorenal effects of liposomal-encapsulated and free griseofulvin administration in rats

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ABSTRACT

Griseofulvin is an oral antifungal agent used for dermatophyte infections, but prolonged use may be associated with hepatic and renal adverse effects. This preclinical study compared the hepatorenal safety profile of free-form griseofulvin and liposome-encapsulated griseofulvin in male Sprague Dawley rats. Griseofulvin-loaded liposomes were prepared using the proliposome hydration method. Fifty-six rats were randomly allocated into two treatment arms: free-form griseofulvin and liposome-encapsulated griseofulvin. Each arm contained four dose subgroups (0, 1, 10, and 100 mg/kg; n = 7 biological replicates per subgroup), administered orally once daily for 14 days. Biochemical markers of renal and liver function (BUN, creatinine, AST, ALT, and ALP) were analyzed using an automated clinical chemistry analyzer, and liver and kidney tissues were evaluated histologically using hematoxylin and eosin staining. Free-form griseofulvin increased BUN at 10 and 100 mg/kg and increased creatinine, AST, and ALT at 100 mg/kg ($p < 0.05$). In contrast, liposome-encapsulated griseofulvin produced lower BUN and AST values than the equivalent free-drug doses and did not produce observable kidney lesions. Histology showed hepatic necrosis and renal congestion in free-drug groups, whereas liposome-encapsulated griseofulvin produced milder hepatic changes only at the highest dose. Because ALT values were not strictly dose-linear and liposome physicochemical characterization was not performed in the present experiment, the findings should be interpreted as preliminary safety evidence rather than definitive pharmacokinetic or efficacy proof.

Keywords: *Griseofulvin; liposome; hepatotoxicity; nephrotoxicity and histopathology*

INTRODUCTION

The rising incidence of mycoses has underscored the need for antifungal agents that are effective while maintaining an acceptable safety profile. Although many antifungal agents demonstrate in vitro activity, their clinical usefulness depends on pharmacological exposure, host immune status, therapeutic window, treatment duration, and adverse-effect burden (de Oliveira et al., 2022; Hakim, 2022).

Griseofulvin (GF) (Figure 1), is a lipophilic antifungal compound originally derived from Penicillium griseofulvum. It is clinically used for dermatophyte infections and acts mainly by interfering with fungal microtubule function and mitotic spindle formation (Tan et al., 2016; Yu et al., 2024). Despite its established utility, prolonged exposure has been linked to abnormal liver function tests, proteinuria, leukopenia, protoporphyria, and hepatotoxicity in experimental settings (Somchit et al., 2004; Yang et al., 2021; Yu et al., 2024).

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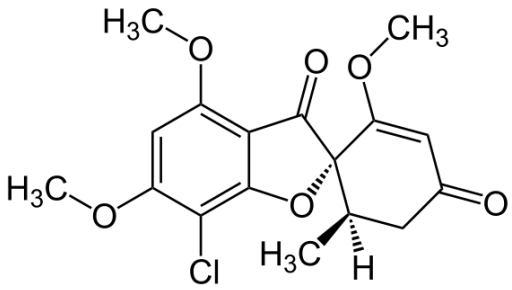
Liposomes are biocompatible phospholipid vesicles that can encapsulate hydrophilic and lipophilic molecules within their aqueous core, bilayer, or bilayer interface. Liposomal delivery has been used to improve drug solubility, alter biodistribution, protect active molecules from degradation, and reduce exposure of sensitive normal tissues to toxic drugs (Mohanraj & Chen, 2006; Nsairat et al., 2022; Sharma & Sharma, 1997). Liposomal amphotericin B is a clinically relevant example in antifungal therapy, demonstrating how lipid-based delivery can reduce toxicity compared with conventional formulations (Couvreur & Vauthier, 2006).

Therefore, this study evaluated whether liposomal encapsulation reduces the hepatic and renal toxicity of griseofulvin after repeated oral administration in rats. The revised manuscript now emphasizes that this is a preliminary toxicity comparison and that future studies must confirm formulation characteristics, pharmacokinetics, and antifungal efficacy before translational conclusions are drawn.

Figure 1

Structure and molecular weight of griseofulvin (MW: 352.77)



METHODOLOGY

Animals and ethics approval

Adult male Sprague Dawley rats (220-250 g) were housed in standard cages at the animal house of the Faculty of Medicine and Health Sciences, Universiti Putra Malaysia. Animals were maintained at room temperature under a 12 h light/12 h dark cycle and provided commercial pellet feed and water ad libitum. The animals were acclimatized for one week before the experiment. Ethical approval was obtained from the Animal Care and Use Committee (ACUC), Universiti Putra Malaysia, approval number UPM/FPSK/PADS/BR-UUH/00445.

Experimental design and treatment groups

A total of 56 rats were randomly divided into two treatment arms: free-form griseofulvin (FF) and liposome-encapsulated griseofulvin (LE). Each arm contained four dose subgroups (0, 1, 10, and 100 mg/kg; n = 7 animals per subgroup). The FF 0 mg/kg subgroup received vehicle control, whereas the LE 0 mg/kg subgroup received blank liposome prepared using the same proliposome procedure without griseofulvin. This clarification was added to identify the blank-liposome control group.

All treatments were administered orally once daily for 14 consecutive days. On Day 15, blood was collected under anesthesia for biochemical analysis, after which rats were euthanized and liver and kidney tissues were harvested for histopathological examination. The reported n values represent biological replicates (individual animals), not technical replicates.

Free griseofulvin preparation

Powdered griseofulvin was purchased from Sigma-Aldrich. A stock solution of griseofulvin was freshly prepared in glycerol and diluted with 1% glycerol and distilled water to obtain the required dosing concentrations.

Liposome-encapsulated griseofulvin preparation

Pro-Lipo(TM) Duo, a commercially available proliposome containing unsaturated soybean phospholipids, was used to prepare liposome-encapsulated griseofulvin according to the manufacturer's instructions with modifications adapted from Chiong et al. (2011, 2013). The ratio of griseofulvin solution: Pro-Lipo(TM) Duo: hydration water: dilution water was 0.4 mL:5 g:9.6 mL:25 mL.

Briefly, 0.4 mL of griseofulvin stock solution (500 mg/mL) was added gradually to 5 g of Pro-Lipo(TM) Duo and stirred for 1 h at approximately 100 rpm. The mixture was hydrated dropwise with 9.6 mL distilled water under moderate

stirring and continued for at least 10 h to obtain a loaded liposome suspension. The suspension was then diluted with 25 mL distilled water and stirred for 30 min. Blank liposomes were prepared using the same procedure, except that griseofulvin solution was replaced with 0.4 mL glycerol. The prepared liposome-encapsulated griseofulvin (12.5 mg/mL; 1% glycerol) was stored at 2-8 degrees C for up to one month.

Formulation characterizations note: particle size, polydispersity index, zeta potential, encapsulation efficiency, and stability were not measured in the present toxicity experiment. This limitation has been explicitly acknowledged in the Discussion because it affects reproducibility and mechanistic interpretation.

Biochemical assays

After 14 days of dosing, approximately 3 mL of blood was collected by cardiac puncture into lithium heparin tubes. Samples were centrifuged at 3500 rpm for 15 min to separate plasma. Hemolysis was avoided during collection and processing. Plasma samples were stored at -20 degrees C until analysis.

BUN, creatinine, AST, ALT, and ALP were measured using a Cobas C311 Chemistry Analyzer (Roche Diagnostics). The assays were automated clinical chemistry assays based on manufacturer-validated enzymatic and colorimetric principles for the respective biochemical parameters. All biochemical analyses were performed using plasma from n = 7 biological samples per subgroup.

Histopathological processing and assessment

Liver and kidney tissues from all animals (n = 7 biological samples per subgroup) were fixed in 10% neutral-buffered formalin. Tissues were processed by routine paraffin embedding, sectioned at approximately 4-5 µm, mounted on glass slides, and stained with hematoxylin and eosin (H&E). No special stains or immunohistochemical markers were applied in this study.

Histopathological assessment focused on hepatic and renal abnormalities relevant to drug-induced toxicity. Liver sections were examined for portal and centrilobular architecture, vascular congestion, inflammatory cell infiltration, cellular degeneration, focal inflammation, and necrosis. Kidney sections were examined for renal cortical and corticomedullary architecture, tubular congestion, glomerular appearance, cellular degeneration, inflammation, and necrosis. Representative fields were evaluated at x100 magnification; at least five non-overlapping fields per organ section were reviewed when tissue area permitted. The photomicrographs shown are representative images from each treatment condition.

Statistical analysis

Data are expressed as mean ± standard error of the mean (SEM). For biochemical parameters, n = 7 biological replicates per subgroup were analyzed. The original analysis used one-way ANOVA with Duncan post hoc testing for within-parameter group comparisons, and $p < 0.05$ was considered statistically significant. Because the study compared both treatment formulation and dose, the interpretation was revised to avoid unsupported dose-dependent claims when marker values were not strictly dose-linear. Statistical analyses were conducted using SPSS version 24.0 for Windows.

RESULTS

Biochemical findings

BUN levels increased significantly in rats treated with 10 and 100 mg/kg free-form griseofulvin compared with the control group (Table 1). In contrast, the liposome-encapsulated groups did not show significant BUN elevation, and BUN values at 10 and 100 mg/kg were significantly lower than the equivalent free-drug groups, suggesting reduced renal stress with liposomal delivery. Creatinine (Table 2) was significantly increased only in rats treated with 100 mg/kg free-form griseofulvin. No significant creatinine elevation was observed in the liposome-encapsulated griseofulvin groups. AST (Table 3), increased significantly in the 100 mg/kg free-form griseofulvin group. The 100 mg/kg liposome-encapsulated group showed significantly lower AST than the equivalent free-drug group. ALT (Table 4), increased significantly in the 100 mg/kg free-form griseofulvin group. ALT was lower in the 1 mg/kg liposome-encapsulated group compared with the equivalent free-drug group. However, because ALT did not increase in a strictly dose-linear manner across all free-drug doses, the revised manuscript avoids a broad dose-dependent conclusion. ALP (Table 5), values showed no statistically significant differences across the treatment groups.

Table 1

Blood urea nitrogen levels after 14 days of treatment

Type of drug	0 mg/kg	1 mg/kg	10 mg/kg	100 mg/kg
FF	4.350 ± 0.331	5.200 ± 0.387	6.183 ± 0.322*#	8.383 ± 0.688*#
LE	3.450 ± 0.303	5.167 ± 0.354	4.117 ± 0.285#	4.400 ± 0.236#

*Note: Values are mean ± SEM, n = 7 biological replicates per subgroup. FF = free-form griseofulvin; LE = liposome-encapsulated griseofulvin. *p < 0.05 compared with corresponding control. #p < 0.05 compared with free-form griseofulvin at the same dose.*

Table 2

Plasma creatinine levels after 14 days of treatment

Type of drug	0 mg/kg	1 mg/kg	10 mg/kg	100 mg/kg
FF	41.500 ± 1.057	43.833 ± 0.654	45.000 ± 1.095	51.500 ± 4.537*
LE	38.333 ± 1.961	43.333 ± 0.558	40.167 ± 3.156	45.000 ± 1.265

*Note: Values are mean ± SEM, n = 7 biological replicates per subgroup. *p < 0.05 compared with control.*

Table 3

Plasma aspartate transaminase (AST) levels after 14 days of treatment

Type of drug	0 mg/kg	1 mg/kg	10 mg/kg	100 mg/kg
FF	79.200 ± 4.567	123.817 ± 7.178	123.900 ± 9.790	160.100 ± 44.010*#
LE	78.550 ± 3.233	84.350 ± 3.671	102.717 ± 8.199	102.600 ± 6.853#

*Note: Values are mean ± SEM, n = 7 biological replicates per subgroup. *p < 0.05 compared with control. #p < 0.05 compared with free-form griseofulvin at the same dose.*

Table 4

Plasma alanine transaminase (ALT) levels after 14 days of treatment

Type of drug	0 mg/kg	1 mg/kg	10 mg/kg	100 mg/kg
FF	35.967 ± 1.739	44.567 ± 6.629#	39.267 ± 2.359	55.050 ± 6.781*
LE	35.967 ± 3.310	27.817 ± 5.688#	35.050 ± 4.730	45.033 ± 2.957

*Note: Values are mean ± SEM, n = 7 biological replicates per subgroup. *p < 0.05 compared with control. #p < 0.05 compared with free-form griseofulvin at the same dose.*

Table 5

Plasma alkaline phosphatase (ALP) levels after 14 days of treatment

Type of drug	0 mg/kg	1 mg/kg	10 mg/kg	100 mg/kg
FF	200.500 ± 23.315	205.000 ± 13.148	209.667 ± 6.157	233.500 ± 16.093
LE	142.167 ± 13.666	203.333 ± 12.529	190.167 ± 28.641	219.833 ± 21.547

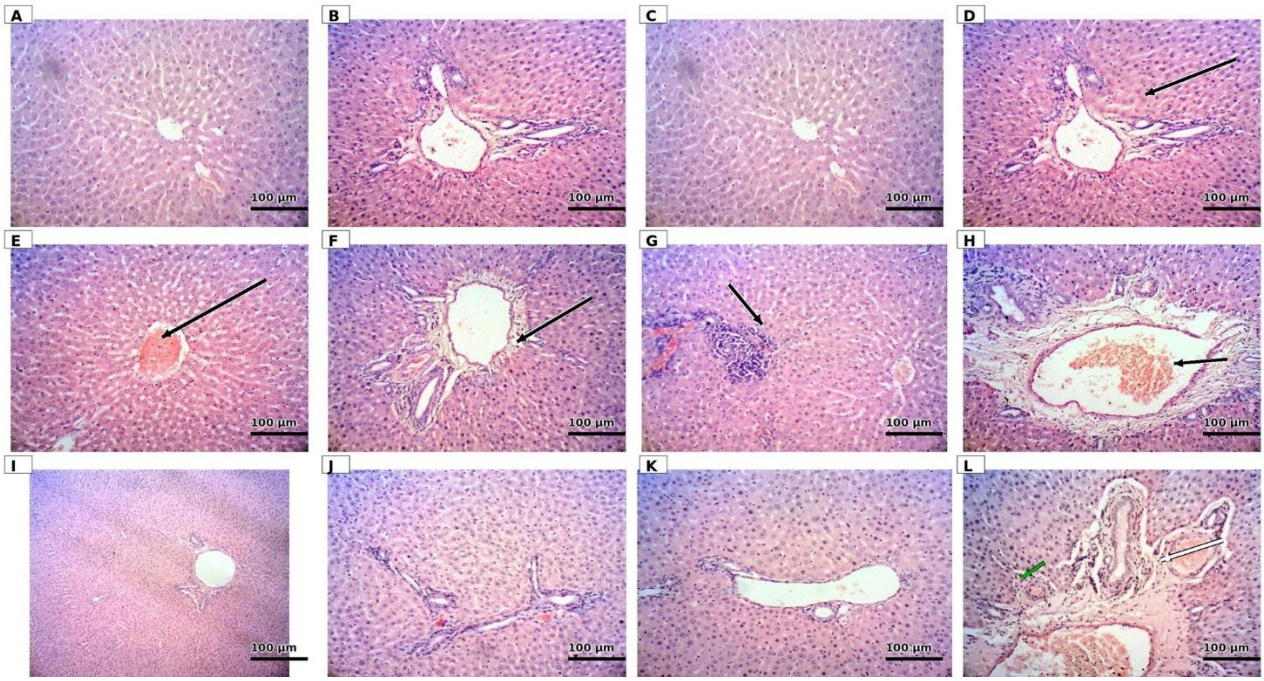
Note: Values are mean ± SEM, n = 7 biological replicates per subgroup.

Histopathological findings

Representative liver photomicrographs are combined in Figure 2 to allow direct comparison between free-form and liposome-encapsulated griseofulvin. Control liver sections showed preserved architecture. Free-form griseofulvin produced mild portal vein congestion at 1 mg/kg, mild central vein congestion and periportal necrosis at 10 mg/kg, and focal inflammation with moderate periportal necrosis at 100 mg/kg. Liposome-encapsulated griseofulvin showed no apparent pathological changes at 0, 1, and 10 mg/kg, whereas mild necrosis and congestion were observed at 100 mg/kg.

Figure 2

Liver histology after 14 days of treatment



Note: Panels A-H show free-form griseofulvin: A, control centrilobular region; B, control periportal region; C, 1 mg/kg centrilobular region with no pathological changes; D, 1 mg/kg periportal region, with the black arrow indicating portal vein congestion; E, 10 mg/kg centrilobular region, with the black arrow indicating central vein congestion; F, 10 mg/kg periportal region, with the black arrow indicating periportal necrosis; G, 100 mg/kg liver section, with the black arrow indicating focal inflammatory cell infiltration; H, 100 mg/kg periportal region, with the black arrow indicating moderate periportal necrosis. Panels I-L show liposome-encapsulated griseofulvin: I, 0 mg/kg blank liposome control; J, 1 mg/kg with no pathological changes; K, 10 mg/kg with no pathological changes; L, 100 mg/kg, with the white arrow indicating mild necrosis and the green arrow indicating congestion. H&E staining, x100. Scale bars = 100 µm; scale calibration should be verified against the original microscope metadata before final submission.

Representative kidney photomicrographs are combined in Figure 3. Free-form griseofulvin produced mild congestion at 10 mg/kg and moderate renal cortical congestion at 100 mg/kg. No observable renal pathology was identified in the liposome-encapsulated griseofulvin groups at the examined magnification.

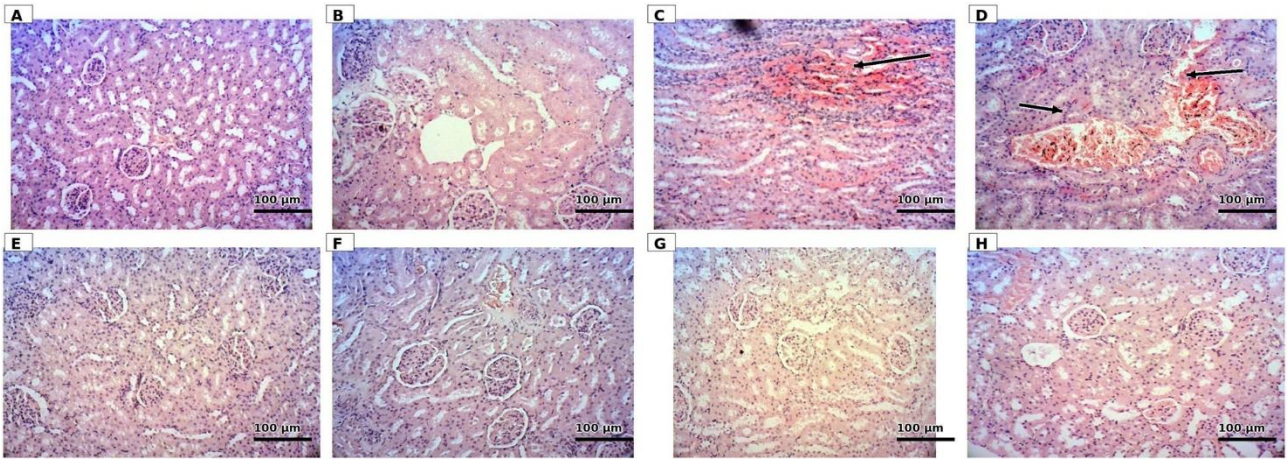
DISCUSSION

This study compared the hepatorenal toxicity profile of free-form and liposome-encapsulated griseofulvin in rats after repeated oral administration. The biochemical and histological data suggest that free-form griseofulvin produced more pronounced hepatic and renal stress than the liposome-encapsulated formulation, particularly at the highest dose. These findings are consistent with the rationale that lipid-based carriers can alter drug distribution and reduce exposure of sensitive tissues (Couvreur & Vauthier, 2006; Sharma & Sharma, 1997).

Renal findings were supported by both biochemical and histological observations. Free-form griseofulvin increased BUN at 10 and 100 mg/kg and increased creatinine at 100 mg/kg. Histological examination showed congestion in the kidney sections of free-drug groups at higher doses. In contrast, liposome-encapsulated griseofulvin did not elevate renal biochemical markers to the same extent and did not produce observable renal lesions in the representative sections examined.

Figure 3

Kidney histology after 14 days of treatment



Note: Panels A-D show free-form griseofulvin: A, control renal cortex; B, 1 mg/kg with no pathological changes; C, 10 mg/kg cortex-medulla region, with the black arrow indicating mild congestion; D, 100 mg/kg renal cortex, with black arrows indicating renal cortical congestion. Panels E-H show liposome-encapsulated griseofulvin: E, 0 mg/kg blank liposome control; F, 1 mg/kg with no pathological changes; G, 10 mg/kg with no pathological changes; H, 100 mg/kg with no observable pathological changes. H&E staining, x100. Scale bars = 100 µm; scale calibration should be verified against the original microscope metadata before final submission.

Hepatic findings also favored the liposome-encapsulated formulation. Free-form griseofulvin increased AST and ALT at 100 mg/kg and was associated with focal inflammation and periportal necrosis. Liposome-encapsulated griseofulvin produced less severe hepatic changes, with mild necrosis and congestion observed only at 100 mg/kg. These results suggest that liposomal encapsulation may reduce, but not completely eliminate, potential hepatic stress.

The revised interpretation is more cautious than the original version. Although several parameters worsened at higher free-drug doses, ALT did not show a strictly dose-linear pattern across all dose groups. Therefore, the manuscript no longer attributes the lower ALT value at 10 mg/kg to undocumented dosing error, and it avoids drawing a definitive dose-response conclusion from inconsistent ALT values. Instead, the finding is treated as a limitation that requires confirmation in a repeated experiment with documented dosing fidelity, predefined exclusion criteria, and observation of post-gavage regurgitation.

The baseline differences between the 0 mg/kg FF vehicle control and the 0 mg/kg LE blank-liposome control for some markers, especially BUN, creatinine, and ALP, may reflect differences between the vehicle and blank-liposome matrices, inter-animal variability, and the small subgroup size. These baseline differences support the need to interpret formulation comparisons using both within-formulation controls and same-dose FF-versus-LE comparisons, rather than relying only on crude baseline values.

The present study also has formulation-related limitations. Although the proliposome method was described, particle size, polydispersity index, zeta potential, encapsulation efficiency, and stability were not measured. Without these characterization data, reproducibility and mechanistic interpretation of the liposomal formulation are limited. Future studies should include full physicochemical characterization and in vitro release testing before in vivo dosing.

Because this work focuses on toxicity, it does not establish whether liposomal encapsulation preserves or improves griseofulvin antifungal efficacy. Liposomal delivery may change intestinal absorption, biodistribution, tissue retention, and elimination. Therefore, future studies should examine pharmacokinetics, tissue distribution, antifungal efficacy against dermatophytes, and comparative therapeutic index before clinical translation is considered.

CONCLUSION

Repeated administration of free-form griseofulvin produced biochemical and histological evidence of hepatic and renal stress in rats, especially at the highest dose tested. Liposome-encapsulated griseofulvin showed a comparatively milder hepatorenal toxicity profile under the same experimental conditions. However, because formulation characterization, pharmacokinetic analysis, antifungal efficacy testing, and verified dosing-fidelity documentation were not included, the findings should be considered preliminary safety evidence. Further studies are required to confirm whether liposomal griseofulvin offers a superior therapeutic index.

AUTHOR CONTRIBUTIONS

Loy Hee San performed the study as part of a BSc project under the supervision of Muhammad Nazrul Hakim. Chiong Hoe Siong, Goh Jun Zheng, and Yong Yoke Keong contributed to the supervision and laboratory analysis of data. Loy Hee San and Muhammad Nazrul Hakim drafted the manuscript. Zainul Amiruddin Zakaria and Mohd Sofian Omar Fauzee reviewed and revised the manuscript critically for important intellectual content. All authors approved the final revised version before submission.

ETHICS APPROVAL

All animal experiments were conducted in accordance with the care and ethical guidelines approved by the Institutional Animal Care and Use Committee, Universiti Putra Malaysia (approval number: UPM/FPSK/PADS/BR-UUH/00445).

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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