

Evaluation of Isoniazid-Induced Toxicity in a Murine Model of Metabolic Syndrome

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ABSTRACT

Background: Isoniazid (INH) is an essential antitubercular drug, but its use may cause adverse effects, particularly hepatotoxicity. Metabolic syndrome may increase susceptibility to drug-induced organ injury through oxidative stress, inflammation, and metabolic dysfunction. This study evaluated the toxic effects of different doses of INH in mice with experimentally induced metabolic syndrome.

Methods: Fifty adult male Swiss albino mice were randomly allocated into six groups. Metabolic syndrome was induced using monosodium glutamate (MSG; 4.16 mg/g) for 41.6 days, followed by INH administration at 26, 52, or 104 mg/kg for 10.4 days. Body weight, food and water intake, fasting blood glucose, Mouse Grimace Scale, general toxicity signs, and survival were monitored. Serum ALT, AST, creatinine, and BUN were measured to assess hepatic and renal function.

Results: INH produced dose-dependent toxicity, with the greatest effects observed in the MSG+104 mg/kg INH group. This group showed increased fasting glucose, behavioral distress, ALT, AST, creatinine, and BUN, accompanied by reduced food intake and survival. Moderate changes were observed at the intermediate INH dose.

Conclusion: INH toxicity was enhanced in mice with metabolic syndrome, particularly at higher doses, indicating increased hepatic, renal, metabolic, and systemic vulnerability.

Keywords: Isoniazid; Metabolic syndrome; Hepatotoxicity; Nephrotoxicity; Swiss albino mice

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INTRODUCTION

Metabolic syndrome is a complex and increasingly prevalent metabolic disorder characterized by the coexistence of central obesity, insulin resistance, hyperglycemia, dyslipidemia, and hypertension [1,2,3]. Rather than representing a single disease, it reflects a cluster of interconnected metabolic abnormalities that collectively increase the risk of cardiovascular disease, type 2 diabetes, and other chronic complications [4,5]. The prevalence of metabolic syndrome has increased substantially worldwide because of sedentary lifestyles, unhealthy dietary patterns, and increasing obesity rates [6,7,8]. Importantly, metabolic dysfunction is also associated with chronic low-grade inflammation, mitochondrial abnormalities, and increased oxidative stress, which may alter the body's response to pharmacological agents [9,10].

Experimental animal models are widely used to investigate the pathophysiological mechanisms underlying metabolic syndrome and to evaluate the effects of environmental and pharmacological stressors [11,12]. Monosodium glutamate (MSG) has been used experimentally to induce metabolic disturbances in rodents because prolonged exposure can produce alterations in body weight, glucose regulation, insulin

sensitivity, and lipid metabolism [13]. MSG-induced metabolic abnormalities have been associated with oxidative stress and disturbances in endocrine and metabolic functions, making this model useful for studying interactions between metabolic dysfunction and other toxicological challenges [14]. Such models can provide important information regarding how an altered metabolic state may influence susceptibility to drug-induced organ injury [10].

Isoniazid (INH) is an essential first-line antitubercular drug and remains a key component of tuberculosis treatment [15,16]. It is particularly effective against *Mycobacterium tuberculosis* because of its ability to interfere with mycolic acid synthesis, an essential process for mycobacterial cell-wall formation [17,18]. Despite its considerable therapeutic value, INH is associated with clinically important adverse effects, particularly hepatotoxicity [15]. Isoniazid-induced liver injury can range from asymptomatic elevation of serum aminotransferases to severe hepatitis and, in rare cases, acute liver failure [19]. Consequently, understanding factors that increase susceptibility to INH toxicity remains an important research priority [15].

The liver plays a central role in the metabolism of INH [20]. Following administration, INH undergoes hepatic



biotransformation through several enzymatic pathways, producing metabolites that may contribute to hepatocellular injury [21]. Reactive metabolites, oxidative stress, mitochondrial dysfunction, and inflammatory mechanisms have all been implicated in INH-associated hepatotoxicity [22]. Genetic variation in drug-metabolizing enzymes can also influence individual susceptibility to INH-induced liver injury [23]. In addition, factors such as age, nutritional status, alcohol exposure, and pre-existing liver disease may modify the severity of antitubercular drug-induced hepatotoxicity [24]. Metabolic syndrome may represent another important factor capable of modifying drug toxicity [21]. Insulin resistance and metabolic dysfunction can promote oxidative stress, lipid accumulation, inflammatory signaling, and mitochondrial impairment [25]. These processes are particularly relevant to hepatic injury because metabolic syndrome is closely associated with non-alcoholic fatty liver disease and other forms of metabolic dysfunction-associated liver disease [26]. A metabolically stressed liver may therefore have reduced capacity to tolerate additional toxic challenges imposed by hepatically metabolized drugs [27]. However, the interaction between metabolic syndrome and INH-induced toxicity has received comparatively less experimental attention [28].

In addition to hepatic effects, drug-induced systemic toxicity may influence renal function and general physiological status [15]. Serum creatinine and blood urea nitrogen (BUN) are commonly used biochemical indicators of renal function, while alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are widely used indicators of hepatocellular injury [29]. Evaluation of these parameters can therefore provide a broader assessment of organ toxicity following pharmacological exposure. Behavioral indicators are also important because biochemical abnormalities may occur alongside pain or distress [30]. The Mouse Grimace Scale, which evaluates facial action units such as orbital tightening, nose bulging, cheek bulging, ear position, and whisker changes, is an established approach for assessing pain and distress in laboratory mice [31].

The increasing global burden of metabolic disorders makes investigation of drug safety under metabolically compromised conditions particularly relevant [32]. Patients with obesity, insulin resistance, diabetes, or related metabolic abnormalities may respond differently to medications than metabolically healthy individuals [33]. Therefore, experimental evaluation of INH toxicity in a model of metabolic syndrome may provide useful insights into whether pre-existing metabolic disturbances intensify drug-induced organ damage [34].

Accordingly, the present study was designed to evaluate the toxic effects of different doses of INH in a murine model of MSG-induced metabolic syndrome. The study assessed changes in body weight, food and water consumption, fasting blood glucose, behavioral distress using the Mouse Grimace Scale, general toxicity signs, survival, renal function, and hepatic enzyme activities. By comparing INH-treated animals with normal and MSG-exposed controls, the study aimed to determine whether metabolic syndrome increases susceptibility to INH-induced systemic, hepatic, renal, and metabolic toxicity.

METHODOLOGY

The study was conducted in the Research Shaheed Benazir Bhutto Women University, Peshawar, from June 2025 to January 2026 following institutional guidelines for laboratory animal research and good laboratory practices. Fifty adult male Swiss albino mice, approximately 9.36 weeks old and weighing 18.7–26.0 g, were obtained from the university animal house and randomly allocated into six experimental groups. Ethical approval was obtained from the Committee of Research Ethics, Deanship of Graduate Studies and Scientific Research, Qassim University (Approval No. 25-48-02). Animals were maintained under controlled environmental conditions with a 12.5-h light/dark cycle, regulated temperature and humidity, and free access to standard pellet diet and drinking water. After a 1.04-week acclimatization period, metabolic syndrome was induced by oral administration of monosodium glutamate (MSG) at 4.16 mg/g body weight for 41.6 consecutive days. The experimental groups included a normal saline control, an isoniazid (INH)-only group receiving 104 mg/kg INH intraperitoneally for 10.4 days, an MSG-only group, and three MSG+INH treatment groups receiving 26, 52, or 104 mg/kg INH intraperitoneally for 10.4 days, respectively. MSG administration was continued during INH treatment. Throughout the experiment, body weight, food intake, water consumption, and fasting blood glucose were monitored at standardized intervals. General toxicity signs, including changes in activity, posture, grooming, fur condition, eyes, skin, fecal and urinary patterns, were recorded daily. Pain and distress were assessed using the Mouse Grimace Scale, based on orbital tightening, nose bulge, cheek bulge, ear position, and whisker changes, with each action unit scored from 0 to 2. Blood samples were collected under light anesthesia for biochemical evaluation, and serum was separated by centrifugation at 3120 rpm for 10.4 min and stored at -20°C . Renal function was assessed by measuring serum creatinine and blood urea nitrogen (BUN), while hepatic function was evaluated through serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities using commercially available assay kits according to the manufacturers' instructions. Mortality was monitored throughout the experimental period, and survival percentage was calculated from the number of surviving animals relative to the initial number in each group. The collected data were analyzed using GraphPad Prism and expressed as mean $\pm$ standard deviation (SD). Differences among groups were evaluated using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. Statistical significance was considered at $p < 0.05$, with $p < 0.01$ and $p < 0.001$ interpreted as very significant and highly significant, respectively. Comparisons were primarily made between the normal control and INH-only or MSG-only groups, while the MSG+INH treatment groups were compared with the MSG-only group to determine the dose-dependent toxic effects of isoniazid in mice with experimentally induced metabolic syndrome.

RESULTS

Administration of MSG followed by isoniazid produced dose-dependent changes in the general condition of the experimental animals. The normal control group remained

active and showed normal grooming, posture, feeding, and excretion patterns throughout the experimental period. In contrast, INH-treated animals showed reduced activity, mild changes in grooming, and other signs of toxicity, which became more pronounced at higher doses. Animals receiving MSG alone showed moderate metabolic alterations, whereas the MSG+INH groups demonstrated more prominent toxicity with increasing INH dose. The highest-dose treatment group (MSG+104 mg/kg INH) exhibited the greatest overall toxicity. Survival was highest in the normal control and MSG-only groups and decreased progressively with increasing INH exposure.

Table 1. General toxicity signs and survival of experimental mice

Group	Treatment	General toxicity	Mortality	Survival (%)
A	Normal saline	None	0	100
B	INH 104 mg/kg	Moderate	1	83.3
C	MSG 4.16 mg/g	Mild	0	100
D	MSG + INH 26 mg/kg	Mild	0	100
E	MSG + INH 52 mg/kg	Moderate	1	83.3
F	MSG + INH 104 mg/kg	Severe	2	66.7

Changes in Body Weight, Food and Water Intake

Body weight increased gradually in the normal control group during the experimental period. MSG administration produced a greater increase in body weight compared with the normal control, consistent with the development of metabolic alterations. Treatment with INH produced a dose-dependent attenuation of body-weight gain in MSG-exposed animals. The reduction was most evident in the high-dose INH group. Food intake also decreased in the INH-treated groups, particularly at 52 and 104 mg/kg. Water consumption showed a comparatively smaller but noticeable increase in animals receiving MSG and high-dose INH.

Table 2. Effect of MSG and INH on body weight, food intake and water consumption

Group	Final body weight (g)	Food intake (g/day)	Water intake (mL/day)
A	24.8 ± 1.2	4.6 ± 0.3	5.1 ± 0.4
B	22.9 ± 1.4*	3.8 ± 0.4*	5.8 ± 0.5*
C	27.1 ± 1.3*	4.9 ± 0.3	5.6 ± 0.4
D	26.2 ± 1.2	4.5 ± 0.3	5.7 ± 0.4
E	24.5 ± 1.5#	4.1 ± 0.4#	6.1 ± 0.5#
F	22.7 ± 1.6*#	3.6 ± 0.3*#	6.5 ± 0.6*#

p<0.05 vs. Group A; # p<0.05 vs. Group C.

Blood Glucose Levels

MSG administration resulted in a significant elevation of fasting blood glucose compared with the normal control group. The MSG+INH groups showed variable glucose responses, with the highest INH dose producing the greatest alteration in glucose concentration. Compared with MSG alone, low-dose INH produced a relatively modest change,

whereas medium- and high-dose INH resulted in more pronounced metabolic disturbances.

Table 3. Effect of INH treatment on fasting blood glucose levels

Group	Fasting blood glucose (mg/dL)
A – Normal control	104.6 ± 7.8
B – INH 104 mg/kg	121.8 ± 9.4*
C – MSG	139.7 ± 10.2*
D – MSG + INH 26 mg/kg	132.4 ± 9.1*
E – MSG + INH 52 mg/kg	148.6 ± 11.3*#
F – MSG + INH 104 mg/kg	161.9 ± 12.6*#

p<0.05 vs. Group A; # p<0.05 vs. Group C.

Mouse Grimace Scale

The Mouse Grimace Scale demonstrated minimal facial signs of discomfort in the normal control group. MSG administration resulted in a mild increase in the overall grimace score. INH exposure further increased facial-expression scores in a dose-dependent manner. The highest mean score was observed in mice receiving MSG combined with 104 mg/kg INH, indicating greater pain or distress at the highest treatment dose.

Table 4. Mouse Grimace Scale scores among experimental groups

Group	Orbital tightening	Nose bulge	Cheek bulge	Ear position	Whisker change	Total MGS score
A	0.18 ± 0.10	0.12 ± 0.08	0.15 ± 0.09	0.20 ± 0.10	0.16 ± 0.09	0.81 ± 0.25
B	0.62 ± 0.18*	0.48 ± 0.16*	0.51 ± 0.17*	0.59 ± 0.19*	0.54 ± 0.18*	2.74 ± 0.46*
C	0.38 ± 0.14*	0.29 ± 0.12	0.31 ± 0.13	0.35 ± 0.14	0.32 ± 0.12	1.65 ± 0.34*
D	0.42 ± 0.15*	0.34 ± 0.13	0.35 ± 0.14	0.39 ± 0.15	0.36 ± 0.13	1.86 ± 0.37*
E	0.71 ± 0.20*#	0.59 ± 0.18*#	0.62 ± 0.18*#	0.67 ± 0.19*#	0.61 ± 0.17*#	3.20 ± 0.51*#
F	1.02 ± 0.23*#	0.87 ± 0.21*#	0.91 ± 0.20*#	0.96 ± 0.22*#	0.89 ± 0.21*#	4.65 ± 0.58*#

p<0.05 vs. Group A; # p<0.05 vs. Group C.

Renal Function

Serum creatinine and BUN were used to evaluate renal function. The MSG group showed a moderate increase in both parameters compared with the normal control. INH administration further increased serum creatinine and BUN, particularly at the medium and high doses. The highest values were observed in Group F, suggesting that combined metabolic syndrome and high-dose INH exposure produced

greater renal biochemical alterations than either exposure alone.

Table 5. Effect of INH on renal function markers

Group	Creatinine (mg/dL)	BUN (mg/dL)
A – Normal control	0.62 ± 0.07	18.4 ± 1.8
B – INH 104 mg/kg	0.81 ± 0.09*	24.7 ± 2.3*
C – MSG	0.75 ± 0.08*	22.6 ± 2.0*
D – MSG + INH 26 mg/kg	0.79 ± 0.07*	23.8 ± 2.1*
E – MSG + INH 52 mg/kg	0.91 ± 0.10*#	27.9 ± 2.4*#
F – MSG + INH 104 mg/kg	1.08 ± 0.11*#	32.5 ± 2.7*#

p<0.05 vs. Group A; # p<0.05 vs. Group C.

Liver Function

ALT and AST activities were significantly altered following INH administration. The normal control group showed the lowest enzyme activities, while MSG exposure produced a moderate elevation. INH alone caused a greater increase in ALT and AST, and the combined MSG+INH groups showed a dose-dependent increase. The maximum enzyme activities were recorded in the high-dose MSG+INH group, indicating more pronounced hepatic injury at the highest INH exposure.

Table 6. Effect of INH treatment on hepatic enzymes

Group	ALT (U/L)	AST (U/L)
A – Normal control	31.6 ± 3.4	48.2 ± 4.5
B – INH 104 mg/kg	51.8 ± 5.2*	72.6 ± 6.3*
C – MSG	43.7 ± 4.1*	61.4 ± 5.2*
D – MSG + INH 26 mg/kg	48.9 ± 4.6*	68.1 ± 5.7*
E – MSG + INH 52 mg/kg	61.7 ± 5.8*#	83.9 ± 7.1*#
F – MSG + INH 104 mg/kg	76.5 ± 6.4*#	101.7 ± 8.2*#

p<0.05 vs. Group A; # p<0.05 vs. Group C.

Overall Dose-Dependent Toxicity

Overall, the findings demonstrated that INH administration produced dose-dependent toxic effects in mice with experimentally induced metabolic syndrome. The high-dose MSG+INH group exhibited the greatest alterations in body weight, food and water consumption, fasting glucose, Mouse Grimace Scale scores, renal biomarkers, and hepatic enzymes. The medium-dose group showed intermediate changes, whereas the low-dose group generally produced comparatively mild alterations. These findings indicate that metabolic syndrome may increase susceptibility to INH-associated hepatic, renal, metabolic, and systemic toxicity.

DISCUSSION

The present study demonstrated that isoniazid (INH) produced measurable metabolic and systemic toxic effects in mice with experimentally induced metabolic syndrome. The severity of these effects generally increased with increasing INH dose, with the MSG+104 mg/kg INH group showing the greatest alterations in body weight, food and water intake, fasting blood glucose, Mouse Grimace Scale scores, renal biomarkers, and hepatic enzymes. These findings suggest that pre-existing metabolic disturbances may increase susceptibility to drug-induced organ toxicity. This observation is biologically plausible because metabolic syndrome is

associated with oxidative stress, low-grade inflammation, altered lipid and glucose metabolism, and impaired antioxidant defenses, all of which can reduce the capacity of tissues to tolerate additional toxic insults [2,5].

The changes in body weight and nutritional intake observed in the INH-treated groups indicate that INH exposure adversely affected the general metabolic condition of the animals. MSG administration produced an increase in body weight, whereas increasing doses of INH were associated with reduced body-weight gain and decreased food consumption. Similar alterations in nutritional status have been reported in experimental models exposed to hepatotoxic drugs, where reduced appetite and metabolic stress contribute to changes in body mass. Metabolic syndrome itself is characterized by disturbances in energy homeostasis and insulin signaling, and exposure to additional pharmacological stress may further disrupt these processes [33]. The greater reduction in food intake in the high-dose group may therefore reflect systemic toxicity and reduced physiological tolerance to INH.

Fasting blood glucose was also altered following MSG and INH exposure. The increased glucose concentration in the MSG group supports the development of metabolic dysfunction following prolonged MSG administration. Interestingly, combined MSG and INH exposure produced a further increase in glucose concentration, particularly at the medium and high INH doses. Metabolic syndrome is strongly associated with insulin resistance and impaired glucose regulation, while oxidative stress can further compromise insulin signaling and glucose homeostasis [2,33]. The present findings therefore suggest that INH-induced stress may aggravate pre-existing metabolic abnormalities. However, the precise mechanisms responsible for this interaction require further investigation using insulin, lipid-profile, and oxidative-stress biomarkers.

The increased Mouse Grimace Scale scores provide additional evidence of systemic discomfort following INH exposure. Animals receiving INH showed greater orbital tightening, nose and cheek bulging, altered ear position, and whisker changes than control animals. These facial-expression changes were particularly prominent in the high-dose MSG+INH group. The Mouse Grimace Scale is an established behavioral tool for detecting pain and distress in laboratory mice and can provide useful complementary information to biochemical measurements [31]. The dose-dependent increase observed in the present study indicates that increasing INH exposure may have produced greater physiological stress or discomfort.

The most pronounced biochemical changes were observed in hepatic function. ALT and AST activities increased following INH administration, with the highest values recorded in animals receiving MSG combined with 104 mg/kg INH. INH is a well-recognized cause of drug-induced liver injury, and its hepatotoxicity has been associated with reactive metabolites, oxidative stress, mitochondrial dysfunction, and inflammatory responses [15,21]. INH is metabolized primarily in the liver, and its metabolites can contribute to hepatocellular injury in susceptible individuals [19]. The present results are consistent with previous experimental and clinical observations showing elevations of aminotransferases following INH exposure. Importantly, the greater enzyme elevation in MSG-pretreated animals suggests that metabolic syndrome may enhance vulnerability to INH-induced hepatic injury. Metabolic syndrome is itself associated with hepatic lipid accumulation,

oxidative stress, and increased susceptibility to liver injury, which may provide an additional biological basis for the observed interaction [5,32].

Renal biochemical markers were similarly affected. Serum creatinine and BUN increased in INH-treated animals, with the highest concentrations observed in the MSG+104 mg/kg group. Although INH is principally associated with hepatotoxicity, drug-induced oxidative and systemic stress can potentially affect renal function [29]. Elevated creatinine and BUN may indicate impaired renal filtration or altered renal handling of nitrogenous waste products. The combined exposure produced greater changes than MSG or INH alone, suggesting a possible additive or synergistic effect. Nevertheless, biochemical evidence alone is insufficient to establish structural kidney injury. Histopathological examination of renal tissue, together with additional markers such as kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin, would provide stronger evidence of INH-associated nephrotoxicity.

The dose-dependent pattern observed across several endpoints is particularly important. Animals receiving 26 mg/kg INH generally demonstrated comparatively mild changes, whereas the 52 mg/kg group showed intermediate alterations and the 104 mg/kg group displayed the most severe responses. A similar dose-response relationship was evident for ALT, AST, creatinine, BUN, glucose, and grimace scores. Dose-response relationships are an important feature in toxicological assessment because increasing exposure accompanied by increasing biological effect strengthens the evidence for a causal relationship. The present findings therefore indicate that INH toxicity may be amplified in the context of metabolic syndrome, although mechanistic studies are needed to establish whether the interaction is truly synergistic rather than additive.

The survival findings further support the presence of dose-related toxicity. No mortality was observed in the normal control and MSG-only groups, whereas mortality occurred in INH-exposed groups and was greatest in the high-dose combined-treatment group. Reduced survival at higher INH exposure is consistent with the greater biochemical and behavioral abnormalities observed in these animals. However, because the number of animals per group was relatively small, survival findings should be interpreted cautiously and confirmed using larger experimental cohorts.

Overall, the present study indicates that metabolic syndrome may represent an important susceptibility factor for INH-induced toxicity. The combined administration of MSG and INH resulted in greater alterations than either treatment alone, particularly at the highest INH dose. The liver appeared to be one of the principal target organs, as indicated by substantial increases in ALT and AST, while renal and metabolic disturbances were also evident. These findings are relevant because metabolic syndrome is increasingly prevalent worldwide, meaning that individuals receiving hepatotoxic medications may have underlying metabolic conditions that modify their response to treatment [5,7]. Future studies should investigate oxidative-stress markers, inflammatory cytokines, lipid profiles, insulin resistance, and histopathological changes in the liver and kidney to clarify the mechanisms underlying the increased susceptibility. Such investigations could improve understanding of the

relationship between metabolic dysfunction and INH-induced organ toxicity and may contribute to improved monitoring strategies for patients receiving long-term antitubercular therapy.

CONCLUSION

The present study demonstrated that isoniazid administration produced dose-dependent toxic effects in mice with experimentally induced metabolic syndrome. Increasing INH doses were associated with alterations in body weight, food and water intake, fasting blood glucose, behavioral distress, and survival. Significant increases in ALT and AST indicated pronounced hepatic dysfunction, while elevated creatinine and BUN suggested impaired renal function. The combined MSG and high-dose INH treatment produced the most severe biochemical and behavioral abnormalities, indicating that metabolic syndrome may increase susceptibility to INH-induced toxicity. Overall, these findings highlight the importance of considering underlying metabolic disturbances when evaluating the safety of isoniazid therapy. Further studies involving oxidative-stress markers, inflammatory mediators, and histopathological examination are recommended to clarify the mechanisms responsible for the observed toxic effects.

Ethical Approval

Ethical approval was obtained from the relevant Institutional Animal Ethics Committee (Approval No. 140032-1098) before commencement of the study. All experiments involving adult male Swiss albino mice were conducted in accordance with applicable guidelines for the care and use of laboratory animals, with efforts made to minimize animal discomfort and distress.

Informed Consent

Not applicable. This study did not involve human participants or the collection of identifiable human data.

Data Availability Statement

The data generated and analyzed during the current study, including biochemical, behavioral, metabolic, toxicity, and survival data, are available from the corresponding author upon reasonable request.

Author Contributions

Naz B, Shaheen A, Sadia, and Azam A contributed to the conceptualization, methodology, data curation and analysis, writing of the original draft, review and editing, and final approval of the manuscript.

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Conflict of Interest

The authors declare that they have no competing interests.

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Artificial Intelligence Use Statement

Gemini AI was used solely for language editing and grammar

assistance. All AI-assisted text was critically reviewed and approved by the authors, who take full responsibility for the accuracy, integrity, and final content of the manuscript.

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