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ORIGINAL ARTICLE

Evaluation of Biochemical and Physiological Alterations Associated with Repeated Therapeutic Paracetamol Administration in Children: Impact on Hepatic Enzymes and Oxidative Stress Biomarkers

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ABSTRACT

Background: Paracetamol is one of the most commonly used antipyretic and analgesic drugs in children. It is safe in recommended therapeutic doses but may affect the metabolism and oxidative balance of the liver after repeated use over a few days. The liver is directly involved in the metabolism of paracetamol, and chronic and/or excessive consumption can affect the enzymes and antioxidant defense systems in the liver.

Objective: To evaluate biochemical and physiological alterations associated with repeated therapeutic paracetamol administration in children, with special focus on hepatic enzymes and oxidative stress biomarkers.

Methods: This descriptive analytical study was carried out in Pak International Medical College Peshawar for period of time January 2023 to June 2023. The children were collected by non-probability consecutive sampling method giving a total of 72 children aged 1–12 years who were taking the same therapeutic dose of Paracetamol for fever or pain. The children were split into three groups based on the number of days Paracetamol was taken: Group A (1-2 days of Paracetamol use), Group B (3-5 days of Paracetamol use) and Group C (>5 days of Paracetamol use). Demographic data, clinical details, paracetamol dosage, frequency, mode and duration of administration were noted. The assessment of physiological parameters, hepatic enzymes, renal function tests, hematological parameters and oxidative stress biomarkers were done. For data analysis SPSS version 25 was used and p value < 0.05 was considered statistically significant.

Results: The mean age of the children was 5.8 ± 2.7 years. Out of 72 children, 40 (55.6%) were male **and** 32 (44.4%) were female. ALT and AST levels increased significantly with longer duration of paracetamol use. ALT increased from 28.6 ± 8.4 U/L in Group A to 46.7 ± 15.8 U/L in Group C, while AST increased from 31.2 ± 9.1 U/L to 52.3 ± 18.4 U/L. Malondialdehyde levels were also significantly higher in Group C, increasing from 2.4 ± 0.7 nmol/mL in Group A to 4.5 ± 1.2 nmol/mL in Group C. Antioxidant markers, including glutathione, superoxide dismutase, catalase, and total antioxidant capacity, showed a significant decline with longer duration of use. Raised ALT, raised AST, increased malondialdehyde, and reduced antioxidant capacity were more frequent among children receiving paracetamol for more than five days.

Conclusion: Repeated therapeutic administration of paracetamol in children was associated with mild but significant alterations in hepatic enzymes and oxidative stress biomarkers, especially when used for more than five days. Although no severe hepatic dysfunction was observed, prolonged or frequent use should be avoided unless clinically indicated. Correct weight-based dosing, caregiver education, and monitoring in selected children with prolonged fever are recommended.

Keywords: Paracetamol, children, hepatic enzymes, ALT, AST, oxidative stress, malondialdehyde, glutathione, antioxidant capacity.

INTRODUCTION

Paracetamol, also known as acetaminophen, is a common medication in pediatrics that is used to treat mild to moderate pain and fever. Doctors routinely prescribe it and it is widely used by parents at home due to ease of access and a sense of safety. For children, dosage is usually calculated on a weight basis, and there are a number of pediatric references that outline therapeutic dosing at approximately 10-15 mg/kg per dose at appropriate intervals with attention to maximum daily dose. Even though this is a very good safety record, it does not mean that biochemical changes can't be increased if the upper level of frequency or prolonged use occurs, or if accidental repeated doses are given [1-3].

Liver is the primary organ involved in paracetamol metabolism. In normal therapeutic conditions, most of the drug is metabolized by glucuronidation and sulfation pathways and a small percentage is converted to the reactive metabolite N-acetyl-p-benzoquinone imine. Typically, this metabolite is detoxified by glutathione. However, on repeated or prolonged exposure to paracetamol, particularly when it is given to children who have fever, low oral intake, dehydration and intercurrent illness, the antioxidant reserve may be depleted. This can result in the elevation of hepatic enzymes with only mild clinical signs of liver injury before the detection of any clinical signs of liver injury [4-6].

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Alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) are enzymes that are found in the liver and are generally considered markers of hepatocellular stress or damage. However, slight elevations of these enzymes can happen along with illness, medication, or low body fluids, and during periods of metabolic stress. When interpreting liver enzymes, it is necessary to be aware of the possibility of biochemical changes in the liver due to repeated paracetamol administration without clinical symptoms. Children can be stable and have laboratory evidence of early hepatic or oxidative alterations. Hence, repeated dose liver enzyme evaluation could be useful in child practice to give information about drug safety [7-9].

The involvement of oxidative stress in hepatotoxicity caused by paracetamol is crucial. Malondialdehyde is a commonly used indicator of lipid peroxidation, while the total antioxidant capacity, glutathione, superoxide dismutase and catalase are indices of antioxidant defense. The increase in malondialdehyde along with a decrease in antioxidant markers indicates an oxidative imbalance shift. In many instances, severe toxicity is thought to be due to overdosing, but repeated therapeutic doses can also affect oxidative stress pathways, especially after several days of therapy. These biochemical changes are significant because they can happen before clinical signs of hepatotoxicity are evident [10-12].

Paracetamol is commonly used by children in Pakistan for fever associated with respiratory infections, gastrointestinal disease, fever associated with the post vaccination period and as a

pain reliever for non-specific pain. Many carers do not calculate the correct dose based on body weight and some may use Paracetamol for several days without consulting a doctor. Information on hepatic enzyme changes and/or oxidative stress biomarkers for children who have used paracetamol for repeated therapy is scanty. Biochemical effects of repeated therapeutic dosing are less often assessed in the typical pediatric practice setting and most attention is given to overdose [13, 14].

Therefore, the present study was conducted at Pak International Medical College, Peshawar, to evaluate biochemical and physiological alterations associated with repeated therapeutic paracetamol administration in children. The study specifically assessed hepatic enzymes and oxidative stress biomarkers in relation to duration and dose of paracetamol use. The findings may help improve rational prescribing, caregiver counseling, and early identification of children who may require monitoring during prolonged antipyretic therapy.

METHODOLOGY

This descriptive analytical study was conducted at Pak International Medical College, Peshawar**, from** January 2023 to June 2023. The study was designed to evaluate biochemical and physiological alterations associated with repeated therapeutic administration of paracetamol in children, with special focus on hepatic enzymes and oxidative stress biomarkers. Written informed consent was obtained from the parents or legal guardians of all participating children after explaining the purpose, procedure, benefits, and possible risks of the study. Confidentiality of all participants was maintained throughout the research process.

Through non-probability consecutive sampling, a total of 72 children who were taking therapeutic Paracetamol repeated doses were included. All children 1 to 12 years of age who were prescribed paracetamol for fever or pain and who had taken it within the therapeutic dose range were included. Therapeutic administration was deemed to be taking paracetamol more than once in the course of 24 hours. The subjects were split into three groups based on the number of days the Paracetamol was given. The children in Group A were those receiving paracetamol for 1 – 2 days, those in Group B for 3 – 5 days and those in Group C for more than 5 days.

Children were selected if they had been given paracetamol in therapeutic doses for fever, respiratory tract infection (RTI), gastrointestinal illness (GI), post-vaccination fever or pain with fever. Children with known chronic liver disease, acute viral hepatitis, chronic renal disease, congenital metabolic disorders, severe malnutrition, history of accidental or toxic paracetamol overdose, systemic illness likely to affect hepatic enzymes or oxidative stress biomarkers and use of antioxidant supplements were excluded. Children for whom parents/guardians did not consent were also excluded from the study.

A structured proforma was used to obtain data. Demographic data such as age, gender, body weight, place of residence and socio-economic status were taken. Clinical information including the type of complaint, indication for Paracetamol use, length of fever or pain, associated diagnosis, history of previous paracetamol use and hospital admission status were recorded. Paracetamol-related information consisted of dose (mg/kg), frequency of administration (times/day), total dose (mg/kg/day), route of administration, and total duration of use. Prescribed dosage confirmed from medication chart, prescription or from parent (where applicable).

Physiological parameters were determined at enrollment. Standard clinical assessments were made in recording body temperature, heart rate, respiratory rate, systolic and diastolic blood pressure, and oxygen saturation. The temperature was taken with a digital thermometer, blood pressure was taken using an age appropriate blood pressure cuff and oxygen saturation was taken by pulse oximetry. These parameters were documented to evaluate the physiological condition of children and to see any clinical modifications with longer use of Paracetamol.

Blood samples were taken from veins using aseptic technique by experienced laboratory personnel. About 3-5 mL blood was collected from each child and stored in the respective tubes for biochemical, hematological and oxidative stress studies. Liver function tests comprised serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin and serum albumin. In addition, renal safety parameters such as serum urea and serum creatinine were also performed. CBC was done to measure hemoglobin, TLC and platelet count.

The cell effects of repeated therapeutic doses of paracetamol were evaluated by measuring oxidative stress biomarkers. The lipid peroxidation marker (malondialdehyde) and the antioxidant defense markers (glutathione, superoxide dismutase, catalase and total antioxidant capacity) were measured. Serum was then separated by centrifugation and stored at the proper temperature for the analysis. Commercial kits were used to measure the biomarkers, following the manufacturer's guidelines. The results were reliable based on the standard laboratory procedures and internal quality control procedures.

Raised liver enzymes were those whose values were above the upper normal limits (age dependent laboratory reference range) for both ALT and AST. Oxidative stress was measured through its increase in malondialdehyde and a decrease in its antioxidant markers: glutathione, superoxide dismutase, catalase and total antioxidant capacity. Alt, AST, MDA, GSH, SOD, catalase and total antioxidant capacity were the primary outcome variables. Secondary variables were bilirubin, albumin, renal function tests, hematological parameters and physiological variables.

All the data were entered and analyzed by using SPSS version 25. The quantitative variables like age, weight, dose of paracetamol, duration of use, hepatic enzymes and oxidative stress biomarkers were given as mean and standard deviation. Qualitative variables like gender, indication for Paracetamol use, route of administration, raised liver enzymes, reduced antioxidant status were presented as frequency and percentage. One way ANOVA was used to compare the three groups for normally distributed quantitative data. Categorical variables were analyzed using Chi-square test. The relationship between hepatic enzymes and oxidative stress markers with duration and dose of paracetamol administration was evaluated using Pearson correlation analysis. A p-value < 0.05 was deemed as statistically significant.

RESULTS

A total of 72 children taking repeated doses of paracetamol were studyied. The mean age of participants was 5.8% ± 2.7% (range 1 to 12 years). Out of 72 children, 40 (55.6%) were male and 32 (44.4%) were female. Paracetamol was used for fever due to RTI or GIT disorder in most children. 24 children in each group were taken: Group A (1-2 days of Paracetamol administration), Group B (3-5 days of Paracetamol administration) and Group C (> 5 days of Paracetamol administration).

Most children were aged 4-6 years. Repeated use of paracetamol occurred most frequently because of clinical problems of the respiratory tract and gastrointestinal illness.

The higher dose of Paracetamol was administered for a longer duration, which resulted in a significant increase in the total Paracetamol dose given in a day. Children who took paracetamol for longer periods had an increased petho-ratio and mean daily dose compared to those who had taken it for shorter periods.

Most of the physiological parameters were similar between the groups. On the other hand, the mean HR was significantly higher in the children taking paracetamol for more than 5 days. This may be because of the duration of fever, the severity of illness or stress and not necessarily due to paracetamol.

An increase was noted in liver enzymes with the duration of paracetamol administration. Children with over 5 days treatment of Paracetamol had a significantly elevated ALTs and AST levels. The amount of direct bilirubin was also found to be significantly

high in Group C while the amount of total bilirubin, serum albumin was not found to be statistically significant.

There was a significant difference between the three groups in their oxidative stress biomarkers. Children who were treated with paracetamol for more than 5 days had the highest malondialdehyde levels, a measure of lipid peroxidation. However, antioxidant markers such as glutathione, superoxide dismutase, catalase and total antioxidant capacity were found to be significantly decreased in the same group.

The children who consumed paracetamol for over 5 days had significantly higher levels of raised ALT, raised AST, increased malondialdehyde, decreased glutathione and decreased TAC. The results indicate that chronic administration of paracetamol may be linked to moderate elevation of the hepatic enzymes, as well as to the occurrence of measurable changes in the level of oxidative stress, particularly when the medication is used for more than 5 days.

The duration of paracetamol use had a positive correlation with ALT, AST and MDA. The antioxidant markers, such as glutathione and total antioxidant capacity (TAc), showed a negative correlation with paracetamol exposure. This suggests a correlation between duration and dose and a rise in hepatic enzyme activity with a corresponding fall in antioxidant defense.

Table 1: Demographic and Clinical Characteristics of Study Participants

Variable	Frequency / Mean	Percentage
Total sample size	72	100%
Age, years	5.8 ± 2.7	—
Age group		
1–3 years	18	25.0%
4–6 years	28	38.9%
7–12 years	26	36.1%
Gender		
Male	40	55.6%
Female	32	44.4%
Main indication for paracetamol use		
Fever due to respiratory infection	34	47.2%
Fever due to gastrointestinal illness	16	22.2%
Post-vaccination fever	10	13.9%
Pain with fever	12	16.7%

Table 2: Pattern of Therapeutic Paracetamol Administration

Variable	Group A: 1–2 Days n=24	Group B: 3–5 Days n=24	Group C: >5 Days n=24	p-value
Mean age, years	5.4 ± 2.5	5.7 ± 2.6	6.2 ± 2.9	0.586
Mean weight, kg	18.6 ± 5.4	19.3 ± 5.8	20.1 ± 6.1	0.672
Paracetamol dose, mg/kg/dose	11.8 ± 1.7	12.4 ± 1.8	13.1 ± 1.9	0.041
Frequency per day	2.6 ± 0.7	3.1 ± 0.8	3.5 ± 0.9	0.002
Total daily dose, mg/kg/day	31.4 ± 7.6	38.2 ± 8.4	45.6 ± 9.1	<0.001
Oral route	22 (91.7%)	21 (87.5%)	20 (83.3%)	0.674
Rectal route	2 (8.3%)	3 (12.5%)	4 (16.7%)	0.674

Table 3: Comparison of Physiological Parameters Among Study Groups

Parameter	Group A: 1–2 Days n=24	Group B: 3–5 Days n=24	Group C: >5 Days n=24	p-value
Temperature, °C	38.1 ± 0.6	38.3 ± 0.7	38.5 ± 0.8	0.148
Heart rate, beats/min	103.5 ± 12.8	108.2 ± 13.6	114.6 ± 14.1	0.024
Respiratory rate/min	25.1 ± 4.2	26.4 ± 4.6	28.2 ± 5.1	0.091
Systolic BP, mmHg	96.4 ± 8.1	95.8 ± 8.4	94.7 ± 8.6	0.763
Oxygen saturation, %	97.6 ± 1.4	97.2 ± 1.6	96.8 ± 1.8	0.219

Table 4: Hepatic Enzyme Profile According to Duration of Paracetamol Use

Hepatic Parameter	Group A: 1–2 Days n=24	Group B: 3–5 Days n=24	Group C: >5 Days n=24	p-value
ALT, U/L	28.6 ± 8.4	34.9 ± 10.6	46.7 ± 15.8	<0.001
AST, U/L	31.2 ± 9.1	38.4 ± 11.8	52.3 ± 18.4	<0.001
ALP, U/L	181.5 ± 42.6	190.8 ± 46.4	204.2 ± 51.7	0.245
Total bilirubin, mg/dL	0.62 ± 0.18	0.68 ± 0.21	0.76 ± 0.24	0.073
Direct bilirubin, mg/dL	0.21 ± 0.07	0.24 ± 0.08	0.29 ± 0.11	0.016
Serum albumin, g/dL	4.1 ± 0.4	4.0 ± 0.5	3.9 ± 0.5	0.318

Table 5: Oxidative Stress Biomarkers Among Study Groups

Biomarker	Group A: 1–2 Days n=24	Group B: 3–5 Days n=24	Group C: >5 Days n=24	p-value
Malondialdehyde, nmol/mL	2.4 ± 0.7	3.1 ± 0.9	4.5 ± 1.2	<0.001
Glutathione, µmol/L	7.8 ± 1.6	6.5 ± 1.4	5.1 ± 1.3	<0.001
Superoxide dismutase, U/mL	8.9 ± 1.8	7.6 ± 1.7	6.4 ± 1.5	<0.001
Catalase, U/mL	42.5 ± 8.7	38.1 ± 7.9	32.6 ± 7.4	<0.001
Total antioxidant capacity, mmol/L	1.42 ± 0.31	1.21 ± 0.28	0.96 ± 0.24	<0.001

Table 6: Association of Duration of Paracetamol Use With Raised Liver Enzymes and Oxidative Stress

Outcome	Group A: 1–2 Days n=24	Group B: 3–5 Days n=24	Group C: >5 Days n=24	p-value
Raised ALT	2 (8.3%)	5 (20.8%)	11 (45.8%)	0.011
Raised AST	3 (12.5%)	6 (25.0%)	13 (54.2%)	0.007
Raised MDA	4 (16.7%)	9 (37.5%)	17 (70.8%)	<0.001
Reduced GSH	3 (12.5%)	8 (33.3%)	16 (66.7%)	<0.001
Reduced total antioxidant capacity	4 (16.7%)	10 (41.7%)	18 (75.0%)	<0.001

Table 7: Correlation of Paracetamol Exposure With Hepatic and Oxidative Stress Markers

Variable Correlation	r-value	p-value
Duration of paracetamol use with ALT	0.46	<0.001
Duration of paracetamol use with AST	0.49	<0.001
Duration of paracetamol use with MDA	0.58	<0.001
Duration of paracetamol use with GSH	-0.52	<0.001
Total daily dose with ALT	0.41	0.002
Total daily dose with MDA	0.55	<0.001
Total daily dose with total antioxidant capacity	-0.48	<0.001

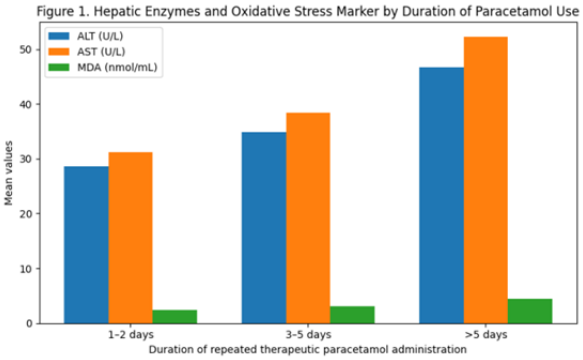

Figure 1 caption: Mean hepatic enzyme levels and oxidative stress marker among children according to duration of repeated therapeutic paracetamol administration. ALT, AST, and MDA showed a progressive increase with longer duration of paracetamol use.

DISCUSSION

Paracetamol is one of the most frequently used antipyretic and analgesic drugs in children because of its easy availability, good tolerance, and wide acceptance in routine pediatric practice. In the present study, repeated therapeutic administration of paracetamol in children was associated with measurable biochemical changes, particularly in hepatic enzymes and oxidative stress biomarkers. Although no child developed severe clinical hepatic dysfunction, children who received paracetamol for more than five days showed higher mean ALT and AST levels compared with those who received it for shorter duration. This finding suggests that even within the therapeutic range, repeated exposure may produce mild hepatic biochemical alteration, especially when administration continues for several days.

This study was an important one because as the duration of taking paracetamol increased, the ALT and AST levels gradually increased. In the children who were given Paracetamol for 1-2 days, ALT was 28.6 ± 8.4 U/L while those who were given Paracetamol for more than five days had ALT of 46.7 ± 15.8 U/L. Similarly, AST increased from 31.2 ± 9.1 U/L to 52.3 ± 18.4 U/L across the same groups. The results suggest that repeated Paracetamol administration is linked to a dose-duration response relationship with the activity of hepatic enzymes. The increase was, however, rather moderate and not accompanied by clinical jaundice, much hypoalbuminemia, or severe liver damage. This confirms that therapeutic use of paracetamol in children is generally safe, but use for prolonged periods and/or multiple doses must be monitored closely, especially when children have an ongoing fever, reduced oral intake of fluid and/or intercurrent illness [15-17].

Liver changes may be understood as a result of the metabolism of Paracetamol. With therapeutic doses, most paracetamol is metabolized by the glucuronidation pathway and the sulfation pathway. A small amount is converted to a reactive metabolite, N-acetyl-p-benzoquinone imine, which normally is detoxified by glutathione. In the case of repeated administration of Paracetamol (particularly for extended periods), glutathione may become relatively depleted. This might lead to higher oxidative stress and account for the slight increase in liver enzymes noted in the present study. A child with fever, dehydration, poor nutritional status or repeated dosing may be more susceptible to these biochemical changes [18].

The pattern of oxidative stress biomarkers was evident in the present study. There was a significant increase in the levels of Malondialdehyde, a marker of lipid peroxidation, with the increased duration of Paracetamol use. It was 2.4 ± 0.7 nmol/mL in Group A, 3.1 ± 0.9 nmol/mL in Group B, and 4.5 ± 1.2 nmol/mL in Group C. However, the antioxidant markers such as glutathione, superoxide dismutase, catalase and total antioxidant capacity were decreased in children who used paracetamol for more than five days. The repeated therapeutic exposure to paracetamol would indicate that repeated paracetamol exposure might alter the balance towards oxidative stress even in the absence of apparent liver damage. A decrease in glutathione is of special importance because glutathione is the primary antioxidant that participates in the detoxification of reactions of the paracetamol metabolites [19].

Correlation analysis confirmed the relationship between exposure to paracetamol and oxidative stress. ALT, AST, MDA levels were positively correlated with duration of Paracetamol use and glutathione and total antioxidant capacity were negatively correlated with Paracetamol use. Likewise, the total daily amount was correlated with increased ALT and MDA levels and decreased antioxidant capacity. The results suggest that the time spent overall exposure and the length of the exposure are significant for biochemical response. These findings do not imply that children should not receive Paracetamol, but highlight that it should be administered appropriately (dose, frequency and duration) [20].

Most of the physiological parameters in this study were similar between the various groups. But the children who had taken paracetamol for over five days had significantly higher heart rate. This may not be a side effect of paracetamol, but could be due to the high fever, dehydration, discomfort or to the illness that paracetamol was being used to treat. There were no statistically significant differences between the groups for temperature, respiratory rate, blood pressure or oxygen saturation. This suggests that the most significant changes were biochemical rather than significant physiological instability.

This study's results have clinical significance as patients usually take Paracetamol at home without medical supervision. Repeated doses may be given several times, various preparations may be used or may be continued for several days during a fever. The children in this study used therapeutic doses, and those using the dose for a longer period were found to have elevated ALT, AST and MDA levels, and decreased antioxidant markers. Hence, caregivers should be trained in proper dosage (based on the body weight of the child), the minimum interval between doses and non-administration of unnecessary excessive doses for a prolonged period. When examining children with fever and mildly elevated hepatic enzymes, the pediatrician should inquire about home medications [21].

There are some limitations in the present study. It was also performed in one center and involved a small number of children (72). The results may not be generalizable because of this limitation. Before paracetamol was administered, baseline liver enzymes and oxidative stress markers were not available for all children, and therefore, it cannot be ruled out that there was pre-existing biochemical variation. Hepatic enzyme changes and mild levels of oxidative stress may also have been due to the underlying disease which was the cause of the fever. Also, long term follow up was not undertaken to see if biochemical changes returned to normal after withdrawal of paracetamol. Multicenter study with larger number of participants and baseline and follow-up biomarker measurement and comparison with non-paracetamol group are suggested for the future.

Overall, the study shows that chronic use of Paracetamol in children could be linked to slight increase in some hepatic enzymes and oxidative stress markers especially after 5 days of therapeutic use. It is concluded that the rational prescribing of Paracetamol, education of caregivers and biochemical monitoring of selected children who need prolonged antipyretic treatment is of importance.

CONCLUSION

Repeated therapeutic administration of paracetamol in children was associated with mild but significant biochemical alterations, especially in those receiving the drug for more than five days. ALT and AST levels increased progressively with longer duration of use, while oxidative stress was indicated by higher malondialdehyde levels and reduced antioxidant markers such as glutathione, superoxide dismutase, catalase, and total antioxidant capacity. No child developed severe clinical hepatic dysfunction, suggesting that paracetamol remains generally safe when used appropriately. However, prolonged or frequent administration, even within therapeutic limits, should be avoided unless clinically justified. Correct weight-based dosing, avoidance of unnecessary repeated use, and careful monitoring in children with prolonged fever or poor general condition are recommended.

REFERENCES

1. Latif AAE, Assar DH, Elkaw EM, Hamza HA, Alkhalifah DHM, Hozzein WN, et al. Protective role of Chlorella vulgaris with Thiamine against Paracetamol induced toxic effects on haematological, biochemical, oxidative stress parameters and histopathological changes in Wistar rats. 2021;11(1):3911 doi.
2. Allam W, Kasem S, Mahmoud S, Abdallah A, Hilal MJASJoFM, Toxicology C. Experimental study of the possible protective effect of alpha-lipoic acid on paracetamol induced oxidative stress and hepatic toxicity in albino rats. 2021;36(1):75-89 doi.
3. Villanueva-Paz M, Morán L, López-Alcántara N, Freixo C, Andrade RJ, Lucena MI, et al. Oxidative stress in drug-induced liver injury

(DILI): from mechanisms to biomarkers for use in clinical practice. 2021;10(3):390 doi.
4. Genfi AKA, Larbie C, Emikpe BO, Oyagbemi AA, Firempong CK, Adjei COJJoE-BIM. Modulation of oxidative stress and inflammatory cytokines as therapeutic mechanisms of Ocimum americanum L extract in carbon tetrachloride and acetaminophen-induced toxicity in rats. 2020;25:2515690X20938002 doi.
5. Nunes BJN-sa-idiwEc, impact e. Ecotoxicological effects of the drug paracetamol: a critical review of past ecotoxicity assessments and future perspectives. 2020:131-45 doi.
6. Motawi TK, Ahmed SA, El-Boghdady NA, Metwally NS, Nasr NNJB. Impact of betanin against paracetamol and diclofenac induced hepato-renal damage in rats. 2020;25(1):86-93 doi.
7. Tenório MCdS, Graciliano NG, Moura FA, Oliveira ACMd, Goulart MOFJA. N-acetylcysteine (NAC): impacts on human health. 2021;10(6):967 doi.
8. Seen SJERoG, Hepatology. Chronic liver disease and oxidative stress–a narrative review. 2021;15(9):1021-35 doi.
9. Baliou S, Adamaki M, Ioannou P, Pappa A, Panayiotidis MI, Spandidos DA, et al. Protective role of taurine against oxidative stress. 2021;24(2):1-19 doi.
10. Ramachandran A, Jaeschke HJA, signaling r. Oxidant stress and acetaminophen hepatotoxicity: mechanism-based drug development. 2021;35(9):718-33 doi.
11. Mohammadnejad L, Soltaninejad K, Seyedabadi M, Ghasem Pouri SK, Shokrzadeh M, Mohammadi HJTR. Evaluation of mitochondrial dysfunction due to oxidative stress in therapeutic, toxic and lethal concentrations of tramadol. 2021;10(6):1162-70 doi.
12. Nogueira AF, Nunes BJES, Research P. Effects of paracetamol on the polychaete Hediste diversicolor: occurrence of oxidative stress, cyclooxygenase inhibition and behavioural alterations. 2021;28(21):26772-83 doi.
13. Arroyave-Ospina JC, Wu Z, Geng Y, Moshage HJA. Role of oxidative stress in the pathogenesis of non-alcoholic fatty liver disease: implications for prevention and therapy. 2021;10(2):174 doi.
14. Ishaq A, Gulzar H, Hassan A, Kamran M, Riaz M, Parveen A, et al. Ameliorative mechanisms of turmeric-extracted curcumin on arsenic (As)-induced biochemical alterations, oxidative damage, and impaired organ functions in rats. 2021;28(46):66313-26 doi.
15. Famurewa AC, Ugwu-Ejezie CS, Iyare EE, Folawiyo AM, Maduagwuna EK, Ejezie FEJD, et al. Hepatoprotective effect of polyphenols isolated from virgin coconut oil against sub-chronic cadmium hepatotoxicity in rats is associated with improvement in antioxidant defense system. 2021;44(4):418-26 doi.
16. Suda N, Cendejas Hernandez J, Poulton J, Jones JP, Konsoula Z, Smith C, et al. Therapeutic doses of acetaminophen with co-administration of cysteine and mannitol during early development result in long term behavioral changes in laboratory rats. 2021;16(6):e0253543 doi.
17. Liu M, Zhang G, Song M, Wang J, Shen C, Chen Z, et al. Activation of farnesoid X receptor by schaftoside ameliorates acetaminophen-induced hepatotoxicity by modulating oxidative stress and inflammation. 2020;33(2):87-116 doi.
18. Khattab A, Taweek A, Abo-EL-Sooud K, Ahmed K, El-Gendy A, Ahmed AJAAVS. Elettaria cardamomum essential oil rescues paraceta-mol-induced hepatorenal damage via modulating oxidative stress in rats. 2020;8(s2):24-33 doi.
19. Ommati MM, Amjadinia A, Mousavi K, Azarpira N, Jamshidzadeh A, Heidari RJS. N-acetyl cysteine treatment mitigates biomarkers of oxidative stress in different tissues of bile duct ligated rats. 2021;24(2):213-28 doi.
20. de Mello Miyasaki AM, Rigobello C, Klein RM, Crespigio J, Flaiban KK, Bracarense AP, et al. Evaluation of hepatic and renal effects in rat dams and their offspring after exposure to paracetamol during gestation and lactation. 2020;32(18):1301-10 doi.
21. Bührer C, Endesfelder S, Scheuer T, Schmitz TJIjoms. Paracetamol (acetaminophen) and the developing brain. 2021;22(20):11156 doi.

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