EFFECT OF MICROPLASTIC INTAKE ON INTESTINAL AND PANCREATIC CELL DAMAGE

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EFFECT OF MICROPLASTIC INTAKE ON INTESTINAL AND PANCREATIC CELL DAMAGE

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ABSTRACT

Introduction: *Microplastics are plastic particles that result from the breakdown of larger plastic particles into smaller pieces and are found in natural environments such as oceans, beaches, and land. Microplastics harm the environment and affect human health. The main entrance of microplastics into the body is the digestive system, through the food and drinks we consume daily. Various investigations have shown that human feces samples contain microplastics that come from ingestion of contaminated food. If it continues, it can damage our body cells.* ***Objective:*** *This research aims to demonstrate that oral administration of microplastics can impair the function of the small intestine, large intestine, and pancreas in rattus of the strain Rattus norvegicus wistar.* ***Method:*** *This study is a quantitative analytic investigation employing an experimental methodology on experimental animals. In this work, the experimental animals were separated into six groups, including the control group and the treatment groups X1, X2, X3, X4, and X5; microscopic observations were conducted 90 days after the microplastics were administered.* ***Results:*** *The comparison of the control group with each exposure group to the small intestine revealed significant results in the Pearson correlation test in groups K with X2, X3, and X4 and the Mann-Whitney difference test in groups K with X2 and X4. Comparing the control group with each exposure group to the large intestine revealed no significant results in the Pearson correlation test and the Mann-Whitney difference test.* ***Conclusion:*** *The correlation test results between the control group and the complete exposure groups revealed significant outcomes in the small intestinal tissue but not in the large intestine and pancreas tissue.*

Keywords: *Microplastics, intestinal cells, pancreatic cells, cell damage*

ABSTRAK

Pendahuluan: Mikroplastik adalah partikel plastik yang dihasilkan dari pemecahan partikel plastik yang lebih besar menjadi potongan-potongan yang lebih kecil dan ditemukan di lingkungan alami seperti laut, pantai, dan daratan. Mikroplastik memiliki dampak negatif terhadap lingkungan dan mempengaruhi kesehatan tubuh manusuia. Pintu masuk utama mikroplastik ke dalam tubuh adalah sistem pencernaan, melalui makanan dan minuman yang kita konsumsi sehari-hari. Berbagai penyelidikan telah menunjukkan bahwa sampel kotoran manusia mengandung mikroplastik yang berasal dari konsumsi makanan yang terkontaminasi. Jika terus berlanjut, bisa merusak sel-sel tubuh

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kita. **Tujuan:** Penelitian ini bertujuan untuk membuktikan bahwa pemberian mikroplastik peroral dapat mengganggu fungsi usus halus, usus besar, dan pankreas pada rattus strain Rattus norvegicus wistar. **Metode:** Penelitian ini merupakan penelitian kuantitatif analitik dengan metodologi eksperimen pada hewan coba. Pada penelitian ini hewan coba dipisahkan menjadi enam kelompok yaitu kelompok kontrol dan kelompok perlakuan X1, X2, X3, X4, dan X5, dan pengamatan mikroskopis dilakukan 90 hari setelah pemberian mikroplastik. **Hasil:** Perbandingan kelompok kontrol dengan masing-masing kelompok paparan usus halus menunjukkan hasil yang signifikan pada uji korelasi Pearson pada kelompok K dengan X2, X3, dan X4 dan uji beda Mann-Whitney pada kelompok K dengan X2 dan X4. Perbandingan kelompok kontrol dengan masing-masing kelompok paparan usus besar menunjukkan tidak ada hasil yang signifikan dalam uji korelasi Pearson dan uji perbedaan Mann-Whitney. **Kesimpulan:** Hasil uji korelasi antara kelompok kontrol dan kelompok paparan lengkap menunjukkan hasil yang signifikan pada jaringan usus halus tetapi tidak pada jaringan usus besar dan pankreas.

Kata kunci: mikroplastik, sel usus, sel pankreas, kerusakan sel.

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INTRODUCTION

The use of plastic has continued to expand dramatically during the past year. In 2020, based on statistical data, global plastic manufacturing reached 367 million tons per year, with Indonesia producing 65,2 million tons. (1)(2). The abundance of plastic production and use is caused by the plastic characteristic itself, such as ease of manufacture, low cost, and durability (3). However, plastic is an inorganic material that cannot be dissolved and can only be degraded by thermal oxidation, ultraviolet light, temperature, and/or mechanical destruction (4).

According to GESAMP, microplastics comprise plastic particles degraded/crushed to 5mm to 1nm (5). The data show that the system for managing plastic waste remains problematic causing a great deal of plastic/microplastic waste was finally dumped into the ocean and dispersed across the marine ecosystem (3)(4). Microplastic contamination in marine ecosystems is proven by the presence of microplastics in the digestive tract of fish, shellfish, seabirds, sperm whales, and other marine species (6).

According to a study, microplastics can enter the human body via the respiratory and digestive systems. Due to

the size and abundance of microplastics, it is easier for them to enter the respiratory tract, particularly for people who work in synthetic textile factories (7). According to studies, many microplastics exist in the foods and drinks we consume daily. Up to 80 MPs/g/day of microplastics can be detected in the seafood, sugar, salt, alcohol, and even drinking water we consume daily (8)(9). The most widely used types of plastic are polyethylene terephthalate, HD polyethylene, polyvinyl chloride, LD polyethylene, and polypropylene.

According to Wright, the primary route for microplastics to enter the body is through the digestive system via foods and beverages we consume daily. Microplastics will pass through the gastrointestinal tract and enter the lymphatics via the slits at the ends of the intestinal villi. In addition, microplastics are hydrophobic, so they prefer to gather and accumulate. Microplastics with smaller dimension can enter the blood stream through phagocytosis on M-cells in Peyer's patches. In addition, microplastics will enter the vascular system and disperse to all human organs and tissues (10). Research shows that microplastics can stimulate the body to induce Reactive Oxygen Species (ROS) which can stimulate genotoxic stress, DNA damage, pro-inflammatory cell activation, and cause cell death (11)(12).

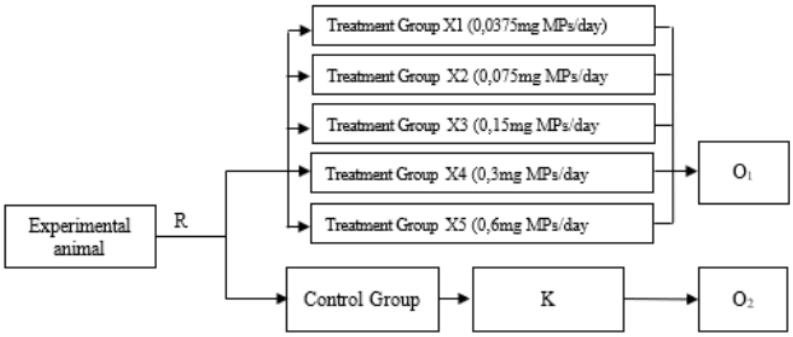
Deng et al. found that the accumulation of microplastics with a size of 5 μm was significantly much more than microplastics with a size of 20 μm after 28 days of exposure. This research also revealed that microplastics could be transferred to other organs/tissues via the vascular system and accumulate in the digestive system. On fluorescent examination, spectroscopy, and histological study of three organs (liver, kidney, and small intestine), significant accumulation occurred in the small intestine (11). However, we could not find any research demonstrating that the accumulation of microplastics in the small intestine can cause intestinal dysfunction or even cell death. No study shows that microplastic accumulation in the small intestine and pancreas can lead to cell dysfunction or death, and affect the functions.

Based on the preceding information, this research is required to demonstrate that oral administration of microplastics can impair the function of the small intestine, large intestine, and pancreas via the mechanisms of inflammation and cell death in rattus of the strain Rattus norvegicus wistar.

MATERIALS AND METHODS

This sort of quantitative analytic study employs an experimental methodology using

animal subjects. This purely experimental study used a control group design with just post-test measures. This design began by dividing the experimental animals into six groups, namely the control group, the treatment group X1, X2, X3, X4, and X5, and then making microscopic observations after administering the treatment to the treatment group for a predetermined amount of time. This design model is depicted in the figure below.



Note:
R : Random
X : Microplastic exposure dose distribution (MPs)
K : No exposure to microplastics (MPs)
O_1 : Observations and measurements in the treatment group
O_2 : Observations and measurements in the control group

In this work, the experimental unit was male white rat wistar strain (Rattus norvegicus strain wistar). The experimental unit selected for this study must meet the inclusion criteria but not the exclusion criteria; otherwise, it will be dropped from the study. The study's inclusion criteria were: Two months old (±1 week) white male rats and weighed between 150 (± 20 grams). While the exclusion criteria were sick white rats as determined by a veterinarian's checkup, the inclusion criteria were healthy white rats. White rats are characterized by their lethargic movement, thick white hair, wounds, and hazy eyes. This study's dropout criteria were rats that died during the research which was determined by the absence of rat vital signs. Thirty white rats (Rattus norvegicus strain wistar) and their reserves were divided into five treatment groups (each with five rats) and one control group (5 rats). Using a random allocation technique, rats were randomly divided into six groups. To guarantee internal validity and prevent bias in this study, the researcher did not know to which group the rats were assigned, so all groups were considered equal.

The independent variable in this study was microplastics concentration (MPs). The dependent variables were intestinal and pancreatic function. The connecting variable was cell damage in the pancreas and

intestines. While the control variables determined in this study were the method of administering microplastics orally using a probe, the microplastic diameter of ≤20 µm, the solvent in the form of aquabides, and the post-exposure evaluation time of 90 days, the experimental variables were the method of administering microplastics orally using a probe, the microplastic diameter of ≤20 µm, and the and post-exposure evaluation time of 90 days.

The following table provides operational definitions of study variables, measurement methods, measuring scales, and measurement outcomes:

No	Variable / Sub-variable	Variable Operational Definition	Measurement Results (Indicators) Variable	How to Measure Variables	Measuring instrument	Measuring Scale
1	Microplastic Dosage (MPs)	The number of plastic particles measuring 20 μm was administered to Rattus norvegicus strain wistar via an oral probe.	The number of plastic particles with a diameter of ≤20 m in milligram units is divided into five experimental doses, namely X1, X2, X3, X4, and X5.	Examined under a microscope and recorded on the laboratory result form.	Scanning electron microscope and milligram scale	Ordinal
2	Changes in the morphology of pancreatic tissue	The degree of morphological changes of pancreatic tissue in histopathological preparations with HE staining, which indicates the occurrence of injury, consists of 4 components of a semiquantitative assessment, namely necrosis, formation of vacuoles in acinar cells, degree of inflammation,	The total score for the four assessment components is as follows: 1. Necrosis: no necrosis (score 0), <10% necrosis (score 1), 10%-40% necrosis (score 2), >40% necrosis (score 3). 2. Formation of vacuoles in acinar cells: none (score 0), <20% acinar cells containing vacuoles (score 1), 20%-50% acinar cells containing vacuoles (score 2), >50% acinar cells containing vacuole (score 3)	Observed under a binocular light microscope and recorded the resulting form	Binocular light microscope.	Ordinal

		and acinar edema.(13).	3. Inflammation degree: none (score 0), inflammation in the interlobular area (score 1), inflammation in the intralobular area (score 2), inflammation in the inter-acinar area (score 3) . 4. Acinar edema: none (score 0), interlobular edema (score 1), intralobular edema (score 2), interacinar edema (score 3).			
3	Changes in the morphology of the small intestine tissue	The degree of changes in the morphology of the small intestine tissue on histopathological preparations with HE staining indicating the occurrence of injury was categorized into a score of 1-5 according to the scoring system used in previous studies.(14).	The assessment uses a scoring system, as follows: 1. Score 1: mild inflammatory cell counts in the mucosa. 2. Score 2: mild inflammatory cell counts in the mucosa and submucosa. 3. Score 3: moderate inflammatory cell count in the mucosa and submucosa, accompanied by slight shortening of the villi. 4. Score 4: dense inflammatory cell infiltration and submucosal lymphoid aggregation, accompanied by moderate	Observed under a binocular light microscope and recorded on the results form.	Binocular light microscope	Ordinal

			shortening of the villi. . 5. Score 5: dense to transmural inflammatory cell invasion, accompanied by villous atrophy and crypt damage			
4	Changes in the morphology of the colon tissue	The degree of changes in the morphology of the colon tissue on histopathological preparations with HE staining, which indicates the occurrence of an injury process, is categorized into a score of 1-4 according to the scoring system used in previous studies.(14).	The assessment uses a scoring system, as follows: 1. Score 1: mild inflammatory cell counts in the mucosa. 2. Score 2: mild inflammation of the inflammatory cells in the mucosa and submucosa, accompanied by a minimal decrease in the number of goblet cells. 3. Score 3: moderate inflammatory cell counts in the mucosa and submucosa, accompanied by a decrease in the number of goblet cells and crypt abscesses and/or ulcerations. . 4. Score 4: dense inflammatory cell invasion, may be transmural, accompanied by multiple crypt abscesses and extensive ulceration.	Observed under a binocular light microscope and recorded on the resulting form.	Binocular light microscope.	Ordinal

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Data gathered from histopathological preparations of Rattus norvegicus strain Wistar will be evaluated for completeness and appropriateness. The data was then displayed and analyzed using version 25 of the statistical program for the social sciences. The presentation of univariate data as distribution tables, mean values, and microscopic images. In the meanwhile, bivariate data is displayed via cross-tabulation. Due to the ordinal nature of the examination findings, the statistical analysis was conducted with the SPSS program, specifically the logistic regression test.

RESULTS AND DISCUSSION

Microplastic Exposure Material

This research employs polyethylene plastic. A polymer of low-density polyethylene extracted from food packaging bags. The FCT Z100 miller machine is used to process food packaging bags into a powder of the desired fineness. The resulting plastic powder was then filtered via an 800-mesh sieve. The filtered powder was then inspected using a microscope with a magnification of 400 and a scale of 10 meter.

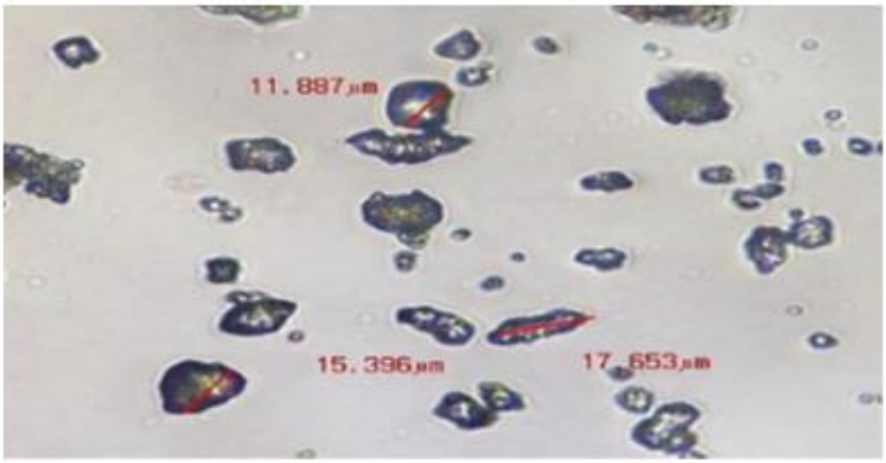

Figure 1. Microscopic picture of polyethylene particles that have been filtered to a size less than 20 μm using the FCT Z100 miller machine.

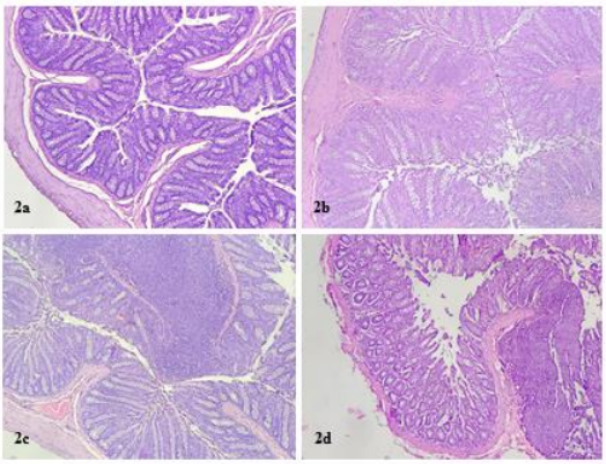

Figure 2. Microscopic view at 400 magnification of the small intestine; a) minimal inflammatory cell infiltration in the mucosa (score 1), b) minimal inflammatory cell infiltration in the mucosa and submucosa (score 2), c) and d) dense inflammatory cell infiltration and submosaic lymphoid aggregation, accompanied by shortening of the villi (score 4)

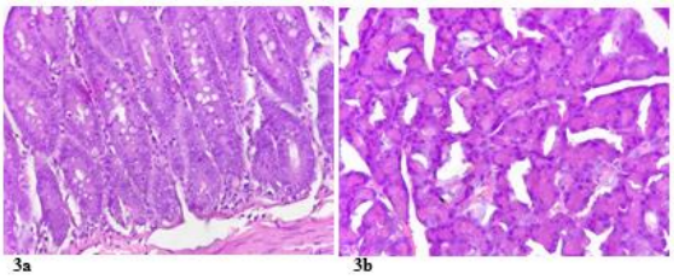

Figure 3. a) Microscopic structure of the large intestine, light infiltration of inflammatory cells in the mucosa, no decrease in the number of goblet cells; b) The microscopic structure of the pancreas, exocrine gland acini did not show significant histologic changes.

Figure 2 and 3 are pictures of the changes found through a microscopic examination with HE staining, then an analysis of the injury process is carried out according to the scoring system. Based on the preceding image, it can be concluded that the microplastics utilized as research exposure materials have a size range of ≤18 μm. Visible microplastic particles are not permeable to light, leading to the conclusion that they are solid particles. Sharp edges can also be noticed on the microplastic particle

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Table 1. Correlation Test and Small Intestine Different Test

No	Comparison Group	Sig Non-Parametric Correlations (2-tailed)	Sig Mann-Whitney (2-tailed)
1.	K-X1	0.173	0.164
2.	K-X2	0.030	0.036
3.	K-X3	0.049	0.054
4.	K-X4	0.019	0.027
5.	K-X5	0.059	0.063

The comparison between the control group and exposure groups X2, X3, and X4 produced significant results (P<0.05), whereas the comparison between the control group and exposure groups X1 and X5 showed nonsignificant results (P<0.05). The findings of the correlation test between the control group and the X2 and X4 exposure groups were statistically significant (P<0.05), indicating that a significant relationship existed. As the correlation test between the control group and the exposure groups X1, X3, and X5 showed insignificant findings (P<0.05), it was determined that there was no meaningful association between the two groups.

Table 2. Frequency and Percentage of Tissue Damage Assessment Grades

Grade	**Control Group n (%)**	**Treatment Group n (%)**
1	3 (42.8)	2 (5.7)
2	3 (42.8)	15 (42.9)
3	1 (14.4)	7 (20)
4	0 (0)	10 (28.6)
5	0 (0)	1 (2.9)

In the control group sample, 42.8% of the sample belongs to grade 1, 42.8% belongs to grade 2, and 14.4% belongs to grade 3, where there are five levels. These results indicate that the control group had varying degrees of damage, with the highest grade being 3. In the exposure group, 28.6% of the samples were from the fourth grade, and 2.9% were from the fifth grade. These data indicate that the damage in the exposure group samples was variable and increasingly severe until it reached grade 5, but the

damage in the control group samples only reached grade 3

Table 3. Correlation Test and Large Intestine Difference Test

No	Comparison Group	Sig Non-Parametric Correlations (2-tailed)	Sig Mann-Whitney (2-tailed)
1.	K-X1	0.109	0.107
2.	K-X2	0.063	0.066
3.	K-X3	0.109	0.107
4.	K-X4	0.552	0.530
5.	K-X5	0.059	0.063

According to table 3, the comparison between the control group and each exposure group did not yield statistically significant findings (P <0.05). Correlation test results were also inconclusive between the control group and the full exposure group (X1-X5).

Table 4. Frequency and Percentage of Grade Assessment of Colon Tissue Damage

Grade	**Control Group n (%)**	**Treatment Group n (%)**
1	0 (0)	0 (0)
2	6 (85.7)	16 (45.7)
3	1 (14.3)	19 (54.3)
4	0 (0)	0 (0)

Based on the information in table 4, it is known that 85.7% of the samples are included in grade 2, and 14.3% of the samples are included in grade 3, which is separated into four assessment components. These results imply that the control group has experienced mild to moderate damage. In this semiquantitative assessment, 45.7% of the samples from the exposure group were in sample grade 2, and 54.3% were in sample grade 3.

Table 5. Correlation Test and Pancreatic Difference Test

No	Comparison Group	Sig Non-Parametric Correlations (2-tailed)	Sig Mann-Whitney (2-tailed)
1.	K-X1	0.179	0.170
2.	K-X2	0.013	0.060
3.	K-X3	0.147	0.141
4.	K-X4	1.000	1.000
5.	K-X5	0.337	0.317
6.	K and X1-X5	0.179	-

According to table 5, the comparison between the control group and each exposure group did not yield statistically significant findings (P <0.05). Correlation test results were also inconclusive between the control group and the full exposure group (X1-X5).

Table 6. Frequency and Percentage of Tissue Damage Assessment Grades

Grade	Control Group n (%)	Exposure Group n (%)
0	0 (100)	1 (2.7)
1	7 (100)	26 (70.3)
2	0 (0)	0 (0)
3	0 (0)	10 (27)
4	0 (0)	0 (0)

In table 6, 100% of the samples are included in grade 1, which consists of four assessment components. These results indicate that the control group has suffered minimal damage. In this semi-quantitative assessment, 27% of grade 3 samples were included in the exposure group.

The part of an organism directly exposed to microplastics is the digestive system, and it is believed that the small intestine is one of the most impacted organs. Several research has demonstrated that one of the harmful effects of a substance is an increase in inflammatory responses in tissues, but other studies have found the opposite[15–17]. Here, histological observations of the small intestine revealed a substantial difference in the degree of inflammatory cell infiltration between the control group and the X-2, X-3, and X-4 exposure groups, and an average tissue damage score was determined. Compared to the control group, the total exposure group experienced more severe symptoms which may be caused by the accumulation of microplastics. This condition has the potential to cause changes at the biomolecular level, such as increased expression of proteins and pro-inflammatory mediators and impaired intestinal cell permeability, which, in the early stages, have not altered the tissue structure to the point where they are recognizable in histology preparations.

The review article by Hirt and Body-Malapel indicated that a decrease in mucus secretion and the transcription factor of the primary gene linked with mucin expression was one of the toxic effects of microplastic accumulation in the colon (Muc-1) [16]. The colon histology in this study showed a slight but non-statistically

significant difference in the degree of tissue damage (including a decrease in the number of goblet cells) between the control and exposure groups because HE staining does not allow for a detailed assessment of mucus secretion, requiring a further study on mucus secretion in the large intestine utilizing PAS staining or immunohistochemistry against Muc-1 antibodies.

There is so little research on the effects of microplastics on the pancreas, particularly in vertebrates, that data on the effects of microplastics on pancreatic tissue are nearly nonexistent. This study found no significant differences in the appearance of exocrine pancreatic tissue between the control and exposure groups. Additional observations of the pancreatic endocrine area can be used as material for further research.

CONCLUSIONS

From the findings about the effect of microplastic feeding on intestinal and pancreatic cell damage, the following conclusions can be drawn:

1. Comparing the control group and each exposure group to the small intestine, the Pearson correlation test in groups K with X2, X3, and X4 and the Mann-Whitney difference test in groups K with X2 produced significant results. In the control group, there was no evidence of damage or light damage; in the exposure group, 42.9% of the samples were grade 2, 20% were grade 3, 28.6% were grade 4, and 2.9% included grade 5.
2. Neither the Pearson correlation test nor the Mann-Whitney difference test revealed any significant differences between the control group and each group exposed to the large intestine. Furthermore, demonstrated that there was moderate to mild damage in the control group. In contrast, 45.7% of the samples in the exposure group were from grade 2, and 54.3% were from grade 3.
3. Comparing the control group to each group exposed to the pancreas, the Pearson correlation test for groups K with X2 and X4 and the Mann-Whitney difference test for groups K and X4 yielded significant results. Furthermore, showed no damage/light damage occurred in the control group, whereas 27% of grade 3 samples were found in the exposure group.
4. The correlation test results between the control group and the entire exposure group (X1-X5) showed significant results in the small

intestine but not in the large intestine and pancreas tissue.

5. The results above show the effect of microplastic administration on damage to small intestinal cells.

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