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Exploring the Protective Effect of Donkey Milk against Indomethacin-Induced Gastric Damage in a Rat Model

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Abstract

The adverse effects of the anti-inflammatory medication indomethacin on the stomach mucosa are well-documented and well-understood. Due to its antioxidant characteristics, high antibody concentration, and minimal allergic traits, donkey milk has lately gained attention as a nutritional supplement. In this research, we looked at Exploring the Protective Effect of Donkey Milk against Indomethacin-Induced Gastric Damage in a Rat Model. The rats were divided into four categories. Standard rat chow was given to the first two categories of rats, whereas 25 mg/kg of donkey milk was given to the third and fourth categories daily through nasogastric gavage. Oral treatment of 30 mg/kg indomethacin on day 11 caused gastric mucosal injury in rats in categories 3 and 4. After 6 hours, every rat was euthanized, and their stomachs were collected for microscopic as well as biochemical analysis of malondialdehyde (MDA) and glutathione (GSH) levels. Immunohistochemistry was used to examine TNF- α expression in the stomach lining. The entire erosion area and the degree of linear ulceration were substantially reduced in the donkey milk-indomethacin category compared to the conventional food-indomethacin category ($p < 0.05$). Additionally, this cohort showed considerable improvements in reduced MDA and increased GSH. Expression of tumour necrosis factor-alpha was greater and more constant in the gastritis group than in the donkey milk group. Donkey milk was shown to have significant protective effects against indomethacin-induced gastrointestinal damage.

Keywords: Protective effect, donkey milk, rat model, indomethacin, gastric damage, rat

Introduction

Any material intended for eradicating or repelling pests is considered a pesticide Donkey milk purported biological qualities have piqued the public's curiosity as a viable nutritional and therapeutic alternative. It's believed that some of the components in donkey milk are similar to those in human milk. Due to its chemical makeup, it may be palatable to those with digestive issues with donkey milk or other milk substitutes. Unlike donkey milk, which may trigger allergy responses in some people, donkey milk has been shown to be hypoallergenic. Milk from a donkey is a good source of protein, carbohydrates, lipids, vitamins, and minerals (1). In addition to containing lysozyme, lactoferrin, immunoglobulins, and antimicrobial peptides, donkey milk is a good source of other bioactive substances. There is speculation that these chemicals are responsible for some of its purported health advantages and immune-enhancing qualities. It has been hypothesized that donkey milk has immunomodulatory and anti-inflammatory properties. It has been said to modify the immunological response, which may lead to less inflammation and a more stable immune system. Antioxidants, such as those found in donkey milk, such as vitamins C and E, help defend against oxidative stress and free radical damage (2). The potential advantages of donkey milk for the skin have led to its usage

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in cosmetics. It may help those with dry or sensitive skin since it hydrates, nourishes, and calms them. Although preliminary evidence for the health advantages of donkey milk is promising, further it is required to fully understand its potential benefits and confirm its effectiveness and safety in various settings. To verify the outcomes shown in the lab and with animals, human clinical trials are essential. Loss of intestinal epithelial barrier function (IEBF) caused by non-steroidal anti-inflammatory medicines (NSAIDs) has been linked to oxidative stress. Indomethacin, like other NSAIDs. When there is more ROS generation than the antioxidant defense systems in the body can deal with, oxidative stress occurs (3). The NSAID metabolism and activation in the digestive system. Lipids, proteins, and DNA are all susceptible to oxidative damage from these ROS. The intestinal epithelial barrier, oxidative stress may compromise the health of the intestinal epithelial cells and their ability to operate normally and remain intact. Tight junctions, specialized structures that keep the barrier functioning by closing gaps between neighboring cells, might be damaged. Gut permeability is enhanced when tight connections are disrupted, enabling potentially hazardous chemicals to cross the gut barrier and reach the underlying tissues (4). The truthfulness of the intestinal epithelial barrier may be compromised by oxidative stress, which can alter the activity and expression of numerous signaling pathways. Some of these factors include inflammation and the activation of pro-inflammatory signaling pathways like NF-kB, both of which may contribute to IEBF decline. The disruption of IEBF caused by NSAIDs is mostly due to oxidative stress. Protecting the intestinal epithelial barrier and decreasing the negative effects of NSAIDs on gut health may be possible using strategies that reduce oxidative stress or boost antioxidant defenses (5). The non-steroidal anti-inflammatory medicines (NSAIDs) are a primary cause of stomach damage of them, indomethacin (Indo) is known to be more likely to cause stomach damage than other NSAIDs. But grapes, berries, and certain therapeutic plants contain piceatannol (PIC), a natural polyphenolic stilbene. PIC's antioxidant and anti-inflammatory properties have been studied for their potential health benefits. Piceatannol's antioxidant qualities come from its capacity to quench reactive oxygen species (ROS) and reduce oxidative stress. This may help prevent NSAID-induced stomach injury by protecting cells from oxidative stress (7). The inflammatory response to stomach damage may be reduced thanks to piceatannol's anti-inflammatory effects. It may sound inferior to the generation of inflammatory mediators by blocking the activation of pro-inflammatory signaling pathways like NF-B. Piceatannol's potential protective benefits against stomach damage from NSAIDs like indomethacin stem from its powerful antioxidant and anti-inflammatory capabilities. Piceatannol may reduce the harmful effects of NSAIDs on the stomach mucosa by lowering oxidative stress and inflammation. Piceatannol's properties make it an intriguing research subject. Still, it is effective and safe in the context of NSAID-induced gastric injury (8). Donkey milk's potential as a dairy product, food additive, and possible therapy for human ailments, including cancer, have all been researched. However, it must be emphasized that the quantity of relevant scientific data is low. The Chemical Makeup of Foods Milk from a donkey contains sugars and proteins and lipids and vitamins, and minerals, much like human milk. The curious about its possible health advantages because of its novel makeup and bioactive chemicals. Several bioactive components in donkey milk may

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contribute to its immunomodulatory effects. These include lactoferrin, lysozyme, and immunoglobulins. It may be significant in cancer and other disorders where immune regulation is crucial (9). Antioxidants like those found in donkey milk (vitamins C and E) help minimize cellular damage and fight against oxidative stress. Cancer is only one of several illnesses thought to have links to oxidative stress. There is evidence from a few researches that donkey milk has anti-inflammatory qualities, which might be useful in treating disorders like cancer that include persistent inflammation. Despite these encouraging signs, it's important to remember that research on the benefits of milk as a dairy alternative is motionless in its infancy. For these advantages to be confirmed and the optimal uses, dosing, and safety factors to be identified, rigorous clinical research, including randomized controlled trials, are required (10). Cadmium is toxic to humans at high enough concentrations. Different authorities agree that cadmium is carcinogenic to humans due to its toxicity. The kidneys are particularly vulnerable to cadmium toxicity. Long-term exposure may lead to renal dysfunction, kidney damage, and, ultimately, kidney failure when it accumulates in the kidneys. The accumulation of cadmium in bones may potentially disrupt bone metabolism. Bone mineral density decreases, fracture risk rises, and skeletal abnormalities are all possible outcomes. Lung inflammation, chronic bronchitis, and potentially lung cancer have all been linked to inhalation of cadmium-containing dust or fumes (11). Hypertension, atherosclerosis, and an elevated risk of heart attack have all been linked to chronic cadmium exposure, according to some research. Reduced fertility, disturbed hormonal balance, and possible impairment of embryonic development are only some negative impacts on reproductive health linked to cadmium exposure. Washing your hands before eating may help reduce the exposure to cadmium, as does eating a healthy, well-balanced diet emphasizing fresh, organic produce. Reducing cadmium release into the environment also requires attention to worker safety and the correct disposal of cadmium-containing trash. There are restrictions on how much cadmium may be used in consumer goods and the workplace all around the globe. These precautions are designed to reduce the dangers of cadmium exposure to humans (12).

Donkey milk's composition is comparable to human milk's, and it has certain potential biological features, including anti-inflammatory, antioxidant, anti-aging, antimicrobial, and anti-cancer effects, which has led to increased interest in it as a natural nutritional and medical product. Studies on the benefits of drinking donkey milk which has been expanding rapidly in recent years. This research (13) focuses on the potential significance of donkey milk in treating several chronic disorders associated with inflammation, namely, its anti-inflammatory and antioxidative capabilities utilizing in vitro models and animal models. NSAIDs are one of the most aggressive variables contributing to stomach injuries. Compared to other NSAIDs, indomethacin (Indo) showed more promise in stomach damage. Inflammatory indicators are significantly reduced in PIC.

Conversely, PIC increased mucin and PGE2 concentrations. In addition, PIC promotes angiogenesis by elevating the levels of proangiogenic factors. The above findings indicate that PIC (14). Kefir, like other fermented milk beverages, is a drink that has been gaining popularity in recent years. Kefir is made by fermenting milk with kefir grains rather than lactic acid bacteria, as is the case with yogurt. Conventional kefir drinks are made from dairy

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for the lactose-tolerant population, and dairy-free kefir beverages are made from plant-sourced substrates for lactose-intolerant and vegan customers (15). The digestive system (GIT) is the primary entry point for environmental stimuli into the human body. The digestive system, which stretches from the mouth to the genitalia, helps break down food, transports and absorbs nutrients, and protects the body from harmful substances, including poisons, antigens, and infections. Normal digestion activities rely on the gastrointestinal mucosa's careful balancing act between immunological tolerance to nutrients and toxic components. Positive effects on GI homeostasis may be attributed to the immunological responses, gut microbiota, and modulation of barrier function by dietary bioactive peptides (16).

The digestive system is the primary entry point for environmental stimuli into the human body. The digestive system, which stretches from the mouth to the genitalia, helps break down food, transports and absorbs nutrients, and protects the body from harmful substances, including poisons, antigens, and infections. Normal digestion activities rely on the gastrointestinal mucosa's careful balancing act between immunological tolerance to nutrients and toxic components. Positive effects on GI homeostasis may be attributed to the modulation of barrier function, immunological responses, and gut microbiota by dietary bioactive peptides (17). The molecular aspects of neurodegenerative illnesses are studied using the excitotoxic and pro-oxidant molecule quinolinic acid (QUIN). To determine how QUIN influences Nrf2 activation in a hurry. Striatal Nrf2 activation was enhanced 30 minutes after QUIN injection without an accompanying rise in reactive oxygen species (ROS) generation or other changes to the redox cellular state.

Additionally, 30 minutes after QUIN injection, nuclear levels of Keap1 and Nrf2 were elevated, and protein-protein interactions between Keap1 and DPP3 and Keap1 and p62 were augmented. As a final result, we identified striatal neurons as particularly susceptible to Nrf2 activation (18). Due to its anti-inflammatory and antioxidant capabilities, donkey milk can protect the stomach lining from damage. The purpose of this research is to determine whether or not donkey milk may prevent stomach mucosal damage caused by the commonly used NSAID, indomethacin.

Methodology

Data set

This investigation was conducted between “October 2013 and May 2014 in the pathology laboratory at Trakya University Hospital and the experimental laboratory of animals in Edirne, Turkey”. Daily deliveries of fresh, unprocessed donkey milk were secured from Koruköy Farm (Koruköy iftlii, Krklareli).

Animals used in experiments

Animal research facilities at Trakya University offered male Sprague-Dawley rats weighing 280-320 g. The research was given the go-light by Trakya University's local ethics council for animal studies. All rats were housed in a controlled laboratory environment (22-24oC, 60% humidity, etc.). The rats were divided into 4 categories of four. The rats in the first and

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third categories received just rat chow for ten days, whereas those in the second and fourth categories also received 25 mg/kg of donkey milk every day. Milk intake was consistent with reports in the scientific literature (250-1000 ml daily, depending on age). The rats in the third and fourth categories were given indomethacin (30 mg/kg) orally beginning on day 11 to cause stomach injury after 6 hours of indomethacin administration, all of the rats were killed. The mucosal injury was graded macroscopically in all stomachs. The physiology lab received semi of the stomach in -80°C freezers to determine the levels of malondialdehyde (MDA) and glutathione (GSH) in the tissues. All stomachs were examined for mucosal damage and given a macroscopical injury grade. Semi of the abdomen was frozen and sent to the physiology lab could analyze tissue levels of malondialdehyde (MDA) and glutathione (GSH).

Testing for Antioxidants

The stomach tissue sample was homogenized by mixing it with 150 mM KCl. For 10 minutes, tissue from the stomach lining was centrifuged at 2000 g after being normalized. Tissue content malondialdehyde (MDA) levels were measured as a thiobarbituric acid immediate material indicator of lipid peroxidation. A sample volume of 200 L was combined with 0.3 ml of 8.2% sodium dodecyl sulfate, 1.6 ml of 20% acetic acid (pH = 5.7), 0.8 ml of purified water, and 2.7 ml of 1.8% thiobarbituric acid. The mixture was intense for sixty minutes at 95 degrees Celsius. The chemical was added to 6.5 ml of a 16:2 (v/v) mixture of n-butanol and pyridine and 1.2ml of purified water after cooling. Centrifuging the substance was placed at 36°C for 10 min, at 2000 rpm. At 533 nm, the organic layer's absorbance was gauged. Malondialdehyde was quantified using a 1.57 -105 M-1 cm-1 extinction coefficient and represented as nanomoles of MDA per gram of soaked tissue (nmol/g). Then 0.2 ml of dithiobisnitrobenzoate (0.4 mg/ml, 1% sodium citrate) was added to this combination. The concentration was calculated after the optical density at 412 nm was measured. This was in line with Ellman's methodology. A spectrometer operating at 412 nm was used to examine the composition of GSH.

Gastric mucosal injury evaluated macroscopically

All macroscopic assessments were done after scarifying the rats and before transferring the semi of the abdomen to the physiology lab. Hyperemia and hemorrhagic erosions were used to create a semi-quantitative scale with values ranging from 0 to 4. A achieve of 0 indicates healthy mucosa, 0.5 - hyperemia, 1 - mild erosions, 2 - moderate erosions, 3 - strict erosions, and 4 - widespread mucosal lesions (hemorrhagic erosions, hyperemia-vascular congestions) in the stomach. Deterioration of the gastric mucosa was assessed using a clear sheet with one mm2 scale and a dissecting microscope. The ratio of the injured mucosal area to the total mucosal area was recorded. The indomethacin-related injury was quantified as a proportion of complete damage against the non-treatment category.

Damage assessment of the stomach mucosa at the microscopic level

Histological analysis of tissue samples collected from the left lobe of the stomach. Tissues were fixed in paraffin and then sectioned at 5 m width before stain with hematoxylin and

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eosin. Over a microscope, tissue slide were analyzed. Damage to the stomach mucosa was measured on a severity scale from 0 to 3. Mucosal erosion = 1, mucosal and submucosal ulceration = 2, and an ulcer reaching the muscularis propria = 3. Both mucosal and submucosal inflammation were assessed, with scores ranging from 0 to 3 based on the following criteria: None (zero), mild (1), moderate (2), and severe (3).

Evaluation by immunohistochemistry

The stomach mucosal specimen was process in the pathology laboratory for immunohistochemistry, and slices 4 micrometers thick were produced from formalin-fixed and paraffin-embedded tissue blocks. Tissue slides were stained for tumor necrosis factor-α using an automated immunohistochemistry discoloration system and a standard antibody incubation protocol. Scores ranged from 0 (no reaction) to 2 (diffuse, severe reaction) for the intensity of the immunological response.

Examining the Numbers

SPSS 20.0 for Windows was used for all arithmetic analyses. The Kruskal-Wallis test and the Mann-Whitney U-test were used to compare the macroscopic damage score, MDA-GSH parameters, gastric mucosal damage, inflammatory score, and immunohistochemistry data. Statistical significance was assumed at the $p < 0.05$ level.

Results Examination using both light and electron microscopy

A macroscopic assessment revealed no mucosal or submucosal injury in control and two categories. Further 1, 2 and 3 categories had macroscopically apparent erosions and ulcers. Compared to the control category, ulcers in categories 3 and 4 were significantly more common, linear, and severe at the macroscopic mucosal level ($p < 0.05$) shown in (Table 1), (Figures 1, 2 and 3). Conversely, visible mucosal injury in Category 4 was substantially less than in Category 3 ($p < 0.05$).

Table (1): Evaluation of histological reactivity across all cohorts

	Inflammatory score	**Histological gastric mucosal damage**	**Macroscopic mucosal damage**
1	1.26 ± 0.48	1.64 ± 0.19	1.14 ± 0.36
2	1.14 ± 0.36	1.64 ± 0.19	1.00 ± 0.00
3	3.39 ± 0.53	2.00 ± 0.77	2.26 ± 0.47
4	2.26 ± 0.53	1.89 ± 0.53	1.51 ± 0.55
P-value	$< 0.001^{\beta}$ 0.011^{α}	$< 0.001^{\beta}$ 0.009^{α}	$< 0.001^{\beta}$ 0.001^{α}

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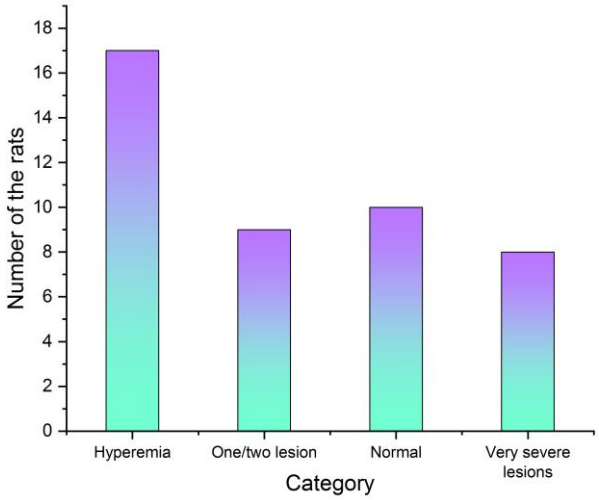

Figure (1): microscopic injury to the stomach mucosa

On microscopic examination, neither Category 1 nor Category 2 had any obvious lesions than sporadic and worrisome hyperemia and edema. In Category 3, deep, widespread ulcers were seen, but in Category 4, mucosal erosions and ulcerations were often restricted to the surface mucosa.

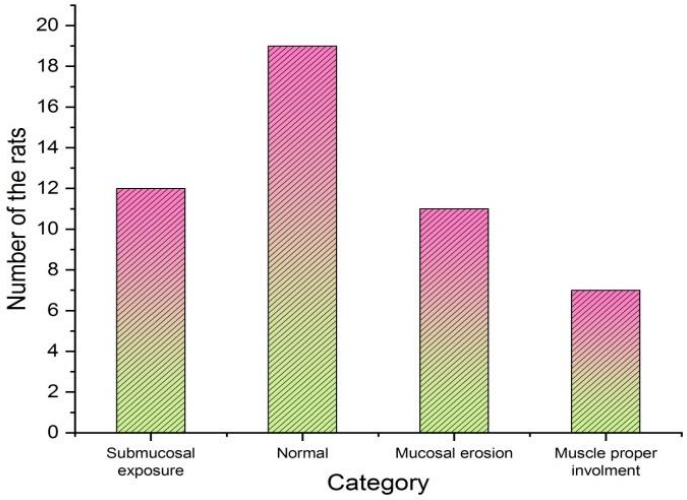

Figure (2): injury to the stomach mucosa on histology

While category 4 had none, category 3 had deep ulcers that extended to the submucosa ($p < 0.05$). Categories 1 and 2 showed no evidence, or very favorable evidence, of mucosal and submucosal inflammation.

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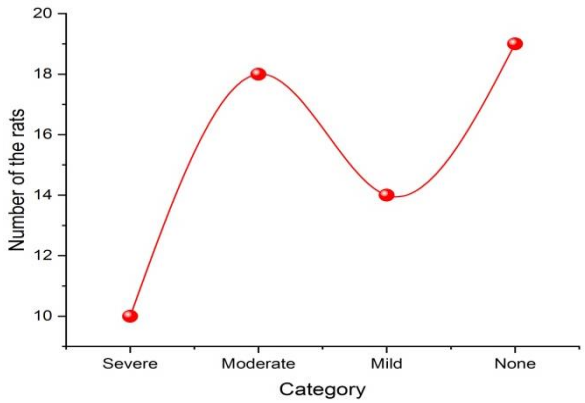

Figure (3): Scale of Inflammation

When comparing categories 2 and 4, category 4 exhibited considerably less irritation overall ($p < 0.05$), with mild to moderate irritation being the norm.

Mucosal MDA and GSH levels in the stomach change

Comparing categories 1 and 3, malondialdehyde concentrations were determined to be 1.13, 1.14 mol/ml and 1.33, 1.15 mol/ml, respectively. According to these results, the indomethacin category had a statistically considerable ($p < 0.05$) rise in MDA concentration in the stomach mucosa. Donkey milk supplemented the regular rat diet in Category 2 rats, resulting in an MDA rate of 0.03, 0.14 mol/ml. There was no discernible deviation from the norm in those rates. MDA levels were 0.20 0.08 mol/ml in category four rats, who were fed the same as category two and were administered indomethacin. Compared to Category 3, this value was substantially lower ($p < 0.05$) shown in (Table 2).

Table (2): Glutathione, tumor necrosis factor, and malondialdehyde levels in all groups

Category's	TNF	GSH	MDA
1	1.21 ± 0.46	1.57 ± 0.15	1.13 ± 0.04
2	1.14 ± 0.36	2.61 ± 0.10	1.15 ± 0.04
3	1.76 ± 0.47	1.96 ± 0.11	1.33 ± 0.05
4	0.89 ± 1.64	1.47 ± 0.22	1.21 ± 0.09
P-value	0.004^{β} 0.012^{α}	0.004^{β} 0.002^{α}	0.003^{β} 0.09^{α}

The entire category had their glutathione levels tested. Category 1 (the controls) had a significantly greater glutathione concentration than Category 3 ($p < 0.05$). Category 2's glutathione levels were not substantially different from those of the control category, whereas Category 4's GSH levels were considerably greater than those of Category 3 ($p < 0.05$). Non-steroidal anti-inflammatory drugs (NSAIDs) like indomethacin are often used for their analgesic and anti-inflammatory effects. However, indomethacin and other NSAIDs have

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been linked to oxidative stress and damage to the gastrointestinal mucosa as a side effect. Since indomethacin therapy was associated with a considerable rise in MDA concentration in stomach mucosa, this finding is suggestive of elevated lipid peroxidation and oxidative stress after indomethacin administration. Oxidative stress may harm cells by interfering with their normal functions and has been linked to mucosal damage and the formation of stomach ulcers.

Expression of TNF- α

In category1 and 2, immunohistochemistry revealed no TNF- α expression outside of extremely faint positives in a few animals. Strong positivity for TNF- α was seen in the indomethacin-induced gastritis category, with statistically considerable differences between that category and the control category ($p < 0.05$). Ulcerated mucosa and the surrounding inflammatory mucosa exhibited particularly significant expression. The expression of TNF- α was lowest in category 4 (Table 2). Initiating and maintaining inflammation are two of TNF- α 's most important functions as a pro-inflammatory cytokine in the control of immune responses. The high levels of TNF- α expression in ulcerated mucosa and the surrounding inflammatory mucosa indicate that this cytokine plays an important role in the inflammatory process, probably aiding in the recruitment and activation of immune cells, inducing inflammation, and possibly exacerbating tissue damage. Since TNF- α may stimulate the production of additional inflammatory mediators and alter the behaviour of cells, it is able to exacerbate the inflammatory response.

Discussion

Anti-inflammatory and pain reliever NSAIDs continue to enjoy widespread global usage. The use of indomethacin in this category is extensive. It is generally recognized, however, that indomethacin may induce gastrointestinal mucosal erosions and ulcers, which severely limit indomethacin's usefulness.(19) The development of indomethacin-induced gastric mucosal lesions is facilitated by producing free lipid peroxide and oxygen radicals. Donkey milk protects against stomach mucosal damage caused by indomethacin, as shown by immunohistochemical and biochemical evidence (20). Lipid peroxidation exacerbates oxidative damage to cells and membranes that plays a significant role in the physiopathology of stomach injury. Catalase, glutathione peroxidase, and Superoxide dismutase (SOD) activities have all been linked to indomethacin-induced damage to the stomach mucosa. Taking medicines that increase the activity of these enzymes to protect the stomach lining against indomethacin is thus the first step towards a remedy (21). Histopathological analysis revealed that when comparing the two indomethacin-exposed categories, rats in category 3 had much more and deeper ulcers than those in category 4; significant finding adds to the growing body of research supporting donkey milk's ability to preserve the stomach mucosa (22). Research shows several compounds have therapeutic and preventative effects against indomethacin-induced stomach ulcers. Particularly well-known for its ability to alleviate symptoms of stomach mucosal oxidative stress and as an antioxidant is selenium. Additionally, both GSH and MDA levels improved after selenium supplementation (23).

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High quantities of lysozyme, lactoferrin, a-lactoglobulin, and immunoglobulin have been observed in donkey milk in several published studies. Such properties protect the digestive tract from infections and other potential irritants (24). In category 4, also given donkey milk, inflammation was drastically reduced compared to category 3. This research provides more proof that drinking donkey milk may help reduce inflammation (25). Activated macrophages are the primary cells responsible for its production, although eosinophils, NK cells, neutrophils, mast cells, CD4+ lymphocytes, and neurons may also accomplish this. Therefore, major work must be put into creating a new marker signaling gastric mucosa inflammation so that NSAID-induced damage to the gastric mucosa may be diagnosed by blood sample without esophagogastroduodenoscopy for long-term NSAID users. There aren't many types of research looking at how donkey milk affects serum TNF- α levels, and none have looked at how it affects TNF- α concentrations in stomach mucosal tissue (26). The high levels of polyunsaturated fatty acids in donkey milk give it powerful antioxidant properties.

Conclusion

The biological characteristics of donkey milk have attracted the public's interest as a potential nutritional and medicinal option. Some of the components of donkey milk may be comparable to those in human milk. For people who have trouble digesting donkey milk or other milk substitutes, its chemical composition may make it more appealing. This study aimed to determine whether or not Donkey Milk might prevent Indomethacin-induced gastric damage in a rat model. The rodents were separated into four groups. The first two groups of rats were fed the regular rat chow, while the third and fourth groups received 25 mg/kg of donkey milk by nasogastric gavage on a daily basis. To investigate TNF- α expression in the stomach lining, immunohistochemistry was used. When comparing the donkey milk-indomethacin group to the regular food-indomethacin group, there was a significant decrease in both the total erosion area and the degree of linear ulceration. The efficiency of the Macroscopic, Histologic gastrointestinal, and inflammatory score was assessed. There has to be more research done to determine whether or not donkey milk has any influence on pro-inflammatory cytokines including COX-2, IL-1, IL-6, IL-8, and IL-17. Our results demonstrated that consuming donkey milk prior to taking indomethacin reduced the severity of damage to the stomach lining caused by the drug. Donkey milk's effects on inflammation caused by bacteria and viruses have only been studied to a limited extent, and the results have been inconclusive.

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