Alkaline Phosphatase on Health

Subjects: Agriculture, Dairy & Animal Science Contributor: Haoming Wu,, Nan Zheng, Jiaqi Wang

Alkaline phosphatase (ALP) is abundant in raw milk. Because of its high heat resistance, ALP negative is used as an indicator of successful sterilization. However, pasteurized milk loses its immune protection against allergies. Clinically, ALP is also used as an indicator of organ diseases. When the activity of ALP in blood increases, it is considered that diseases occur in the viscera and organs. Oral administration or injection of ALP will not cause harm to the body and has a variety of probiotic effects. For infants with low immunity, ALP intake is a good prebiotic, which can protect the infant's intestine from potential pathogens. In addition, ALP has a variety of probiotic effects on any age group, including the prevention and treatment of intestinal diseases, allergies, hepatitis, acute kidney injury (AKI), diabetes, and even the prevention of aging.

ALP infant intestinal health raw milk

1. Introduction

Alkaline phosphatase (ALP) is an enzyme that catalyzes the hydrolysis of phosphate under alkaline conditions. ALP widely exists in various mammalian tissues and plays an important role in biological processes. However, human tissues can also synthesize ALP, including tissue nonspecific alkaline phosphatase (TNAP), placental alkaline phosphatase (PLAP), germ cell alkaline phosphatase (GCALP), and intestinal alkaline phosphatase (IAP) ^[1]. However, for infants with incomplete immune development, ALP gene expression is still low, and exogenous ALP supplementation is very necessary ^[2]. At the same time, ALP protects the health and stability of tissues and bodies at all life stages. When diseases occur, ALP is used as an important biomarker for the diagnosis of many diseases ^{[3][4][5]}.

2. Important Health Indicators

According to clinical diagnosis, abnormal ALP activity in blood is related to various diseases—for example, bonespecific ALP and bone disease ^[3], breast cancer diagnosis ^[4], and diabetes ^[5]. In the case of diagnosis, ALP measured in serum is used as a diagnostic tool for liver disease ^[6] and testicular cancer ^{[7][8]}. In patients with chronic liver disease, blood ALP increased in the order of chronic hepatitis (CH), liver cirrhosis (LC), and hepatocellular carcinoma (HCC) with pathological progress ^[9]. At the same time, ALP in the patient's blood will be detected before and after a medical process. The change in ALP in blood can affect the therapeutic effect and survival rate of patients, such as metastatic prostate cancer ^[10], metastatic breast cancer ^[11], clear cell chondrosarcoma ^[12], and metastatic nasopharyngeal carcinoma ^[13].

3. Factors Affecting ALP Activity

IAP has an important protective effect on the infant intestine. IAP is a homodimer, and each subunit consists of two Zn^{2+} and one Mg²⁺ ion ^[14]. The activity of IAP was the highest at pH 9.7 ^[15]. IAP is generally secreted in the duodenum, followed by less expression in the jejunum, ileum, and colon ^{[16][17][18]}. IAP is largely absent in the stomach in an acidic environment ^{[18][19]}. IAP mainly exists in lumen vesicles secreted by intestinal cells on the brush edge of microvilli. At the same time, a small amount of IAP will also be bidirectionally released into the blood and lumen and then spread throughout the intestine ^[20]. The investigation found that the level of IAP activity in human intestinal tract varies with blood type. The level of IAP in human intestinal tract of type O and type B is the highest, while the activity in human intestinal tract of type A blood is the lowest ^[21]. In the gut, IAP is a mucosal defense factor that restricts bacteria from crossing the mucosal barrier into mesenteric lymph nodes ^{[22][23]}. In addition to the local activity of IAP in intestinal mucosa, about 1–2% of IAP is released into the blood or gastrointestinal cavity to treat and prevent systemic infection and sepsis ^[24].

IAP activity is related to dietary nutrition and dietary frequency. Food intake can regulate the activity of IAP. Intake of omega-3 fatty acids can reduce the level of LPS and improve intestinal permeability by increasing the activity of intestinal IAP in transgenic mice ^[25]. In addition, a protein diet may reduce the activity of IAP. When feeding calves before rumination with a soybean diet, the activities of intestinal enzymes such as IAP in the intestine are reduced $^{[26]}$. Another study found that the intestinal IAP activity of pigs increased significantly in the short term after using wheat or barley instead of a milk-based high protein diet [27]. After the protein structure of milk is destroyed by fermentation, intake of yogurt can increase the activity of IAP ^[28]. In addition, glucomannan, oligosaccharide, and vitamin D supplementation are associated with increased intestinal IAP activity ^{[29][30][31]}. Some phytochemical components, such as curcumin, black pepper, red pepper, ginger, piperine, and capsaicin, have also been found to be associated with increased IAP activity [32]. When mice were fasted for two days, IAP expression in the intestine decreased significantly, resulting in a decrease in the ability of intestinal LPS dephosphorylation ^[23]. Because starvation leads to the downregulation of IAP, the host's sensitivity to pathogens increases. Therefore, for the treatment and prognosis stage of patients, intake of diet that can increase IAP is of positive significance for the recovery of patients' health ^[23] because IAP is associated with limiting the speed of fatty acid transmembrane transport to intestinal cells [33][34]. HFD feeding increases IAP stress-induced secretion in the intestine, thereby maintaining host weight stability ^[35]. On the other hand, some studies have found that HFD feeding can reduce IAP activity and increase TLR4 activity in the intestine of obese rats [36]. Similarly, when present in food ω - 3 PUFA will also lead to a decrease in IAP expression and activity [37]. IAP-KO mice fed HFD were more likely to gain weight ^[33]. Therefore, for different individuals, the effect of HFD feeding on intestinal IAP is not stable, and further research is needed. In addition, protein intake may also be related to the regulation of IAP. The activity of ALP in the intestine of rats fed a protein-free diet decreased by 36-38% [38]. In conclusion, the intake of food nutrition is related to the activity of ALP. Reasonable dietary intake is helpful for regulating the activity of intestinal ALP.

4. Infant Intestinal Health

In Table 1, the research on the prevention and treatment of diseases by ALP are summarized. Relevant studies were identified by searching Web Science, Google Scholar, and PubMed. If a study met the following criteria, it was included in the table: 1. Study and evaluate the effect of oral or injection ALP treatment; 2. Researches written in English until December 2021. All studies that met the requirements of direct ALP treatment of laboratory animals are listed in the table. It turns out that high IAP activity in the intestine of full-term newborns, coupled with the high ALP activity in breast milk in the first few days after birth, provides sufficient detoxification capacity for LPS of initially colonized bacteria ^[2]. After the onset of IBD in infants, TLR4 mRNA expression and protein levels in inflammatory colonic mucosa in children increased [39]. The increased expression of TLR4 may be related to the content of IAP in intestinal mucosa. IAP activity below normal level may lead to IAP/TLR4 imbalance, resulting in increased sensitivity of mucosa to LPS [17]. After treatment, the recovery of intestinal mucosa is very important for the prognosis of the disease. Therapeutic treatment to restore intestinal flora balance may have a significant impact on mucosal healing of IBD ^[40]. In an animal model of colitis induced by sodium dextran sulfate (DSS), exogenous administration of IAP improved the symptoms of colitis [41]. Compared with wild-type mice, IAP-KO mice had more severe colitis induced by DSS ^[24]. In the case of severe intestinal epithelial injury, oral IAP may have beneficial effects [42]. The results obtained in the pediatric population also demonstrate that oral IAP may be beneficial for children with IBD $\begin{bmatrix} 17 \\ 17 \end{bmatrix}$.

Early in life, the initial colonization of intestinal microorganisms will affect the development of intestinal host defense [43][44], and the appropriate development of intestinal tissue may have a far-reaching impact on immune health in infancy and even throughout life ^{[45][46]}. Because the intestinal immune tissue is immature at birth and develops with the initially colonized microorganisms, it has been suggested that the increase in allergy and autoimmune diseases may be caused by the interference of microbial colonization and development of intestinal host defense system [47]. It is worth noting that the host defense capacity of the intestine of preterm infants is particularly immature and that the initial colonization of intestinal microorganisms is not the same as that of normalborn infants [48]. Compared with mature human intestinal cells, infant intestinal cells are more likely to produce excessive inflammatory response when stimulated and even respond to some intestinal symbiotic bacteria with an inflammatory effect [49][50]. The imbalance in intestinal microbial ecology in the neonatal period of preterm infants may lead to excessive intestinal inflammation, resulting in NEC. As the sole source of nutrition for infants, breast milk helps healthy bacterial colonization in the infant's intestines ^[51]. Studies have pointed out that breast milk extruded by preterm mothers can protect the infant's intestine from NEC [52][53]. Although breast milk contains many immune nutrients, such as IgA, oligosaccharides, lactoferrin, ALP, etc., it may help to prevent intestinal inflammation and NEC. At the same time, breast milk may also play an active role in stimulating health-promoting bacteria, thus providing protection against NEC. Studies have pointed out that giving probiotics to preterm infants can also prevent NEC. The combination of probiotics (e.g., Lactobacillus acidophilus and Bifidobacterium bifidum) and human milk has a protective effect, but the combination of probiotics and infant formula has lost its protective effect [54][55].

Compared with infant formula, breast milk has several unique factors to actively protect the intestine of newborns. First, oligosaccharides in breast milk provide an energy source for the intestinal microbiota, help the growth of infant intestinal probiotics, and are beneficial to the infant intestine ^{[56][57]}. Second, breast milk itself contains a

variety of bacteria that actively colonize the intestine, providing protection for the infant's primitive microbiota ^[58]. Third, breast milk contains immunobioactive factors, such as secretory IgA, which can change the colonization of infants' intestines and protect infants from pathogens ^{[59][60]}. Fourth, gastrointestinal administration of exogenous IAP can improve intestinal inflammation and promote intestinal tissue regeneration, while intestinal and systemic IAP administration can reduce systemic inflammation ^[61]. In addition, oral IAP supplements may regulate intestinal metabolic homeostasis by stimulating intestinal IgA secretion ^[4]. In conclusion, breast milk not only can change the intestinal environment of infants to prevent pathogenic bacteria but also can promote the colonization of symbiotic bacteria, so as to promote the short-term and long-term immune health of the host.

IAP can maintain intestinal immune balance and improve host tolerance to symbiotic microbiota by reducing lumen ATP concentration and dephosphorylating bacterial LPS ^[62]. At the same time, IAP knockout mice showed increased fat absorption and obesity, suggesting that intestinal lipid transport is related to the regulation of IAP ^[28]. Both endogenous and oral IAP supplementation can inhibit the absorption of LPS in dietary fat, and oral IAP supplementation can prevent and reverse metabolic syndrome. In addition, IAP supplementation improved the blood lipid status of mice fed standard low-fat food ^{[28][63]}. In animal models of intestinal injury, oral IAP reduces intestinal epithelial injury and inflammation ^[42]. The dynamic transformation of the form of ALP isozyme is related to the maturation of fetal intestine ^[64], suggesting that ALP activity may change during human fetal development. Supplementation of ALP in the intestine of newborn rat pups has a protective effect on experimentally induced NEC ^[65]. ALP has a protective effect on the intestine of premature young rats against intestinal damage and inflammation caused by microbial LPS ^[66].

Intestinal alkaline phosphatase (IAP) can maintain intestinal health through a variety of mechanisms, including detoxification of lipopolysaccharide (LPS), flagellin, CpG DNA and nucleotides; upregulation of the expression level of tight junction protein, thereby increasing intestinal barrier function; and regulation of intestinal microbiome homeostasis ^{[67][68][69]}. During lactation, infant intestinal ALP gene expression and enzyme activity remain low ^[70]. Preterm birth and formula feeding are considered to be associated with the inhibition in IAP expression and activity, and the lack of ALP may increase the risk of NEC ^[71]. For infants, breast milk is the only exogenous source of ALP ^[2], and pasteurization destroys 99% of ALP in breast milk ^[72]. ALP in breast milk is considered to be an anti-inflammatory factor in the neonatal intestine and a key component in inhibiting NEC ^{[73][74]}. The lack of IAP activity will lead to neonatal intestinal ecological imbalance and bacterial translocation, resulting in a variety of diseases ^[75].

In previous studies, it was found that taking LPS can lead to weight gain and acute inflammation and eventually insulin resistance ^[76]. Similar effects can be seen in animal models fed HFD or LPS. Similarly, LPS can also lead to a pro-inflammatory response in the fetal brain after infecting the mother, thereby increasing anxiety and reducing social activities ^[77]. Therefore, researchers believe that the important roles of HFD and LPS in the pathogenesis of ASD seem to be consistent between humans and animals. ALP is considered to be a drug that can protect the balance in the intestinal environment and reduce inflammation ^[78]. ALP has anti-inflammatory effects, prevents intestinal leakage, and promotes a healthy microbiota ^[62]. At the same time, recent studies have proved that oral supplementation of IAP to pregnant mothers is of positive significance to the health of infants. A mouse model test

found that maternal IAP treatment can alleviate some autism spectrum disorder (ASD)-like symptoms of offspring mice ^[79]. It is worth noting that the content of ALP in breast milk decreased with lactation time ^[80]. Therefore, the intake of ALP supplementation for infants and mothers is of great significance for maintaining infant health. Unfortunately, ALP does not exist in any infant formula.

5. Inhibition of Allergy

Children growing up on farms have a lower risk of asthma and allergies than children living in the same rural area but not on farms ^{[81][82]}. This protective "farm effect" is recognized in many people until adulthood ^[83]. The farm exposure associated with this allergic protective effect appears to be eating unprocessed raw milk ^{[84][85]}. In particular, the consumption of raw milk and the protective effect of raw milk have nothing to do with farm conditions, so it can protect the ordinary non-agricultural population ^{[86][87]}. Many studies have shown that eating untreated raw milk can prevent the risk of asthma and allergic diseases ^{[84][85][86][87][88]}. These epidemiological findings recently confirmed the causal evidence that biological milk can prevent allergic asthma caused by household dust mites and OVA-induced food allergy in mouse models ^{[89][90]}.

Pasteurization makes milk lose the ability to protect consumers from allergies. The histone acetylation degree of Th1-, Th2-, and regulatory T cell-related genes in splenocyte CD4+ T cells of rats treated with raw milk was higher than that of mice treated with pasteurized milk. Compared with processed milk products, the histone acetylation degree of Th2 gene in rats treated with raw milk was lower. In the research of mice allergic to food, raw milk reduced allergic symptoms to food allergens other than milk. The activation of T cell-related genes is considered to be the cause of the observed tolerance induction, indicating that epigenetic modification helps raw milk protect the body from allergy ^[90]. On the other hand, some studies have shown that pasteurized milk lost its allergic protection, but pasteurized milk added with ALP restored its allergic protection ^[91]. Skimmed raw milk inhibited food allergy symptoms similar to raw milk and reduced acute skin allergy and lowered levels of OVA-specific Ig-E- and Th-2-related cytokines. This indicates that the fat component is not an ingredient in raw milk that inhibits food allergy ^[91].

ALP can regulate the structure of intestinal microbiota and protect consumers from allergy induction. Raw milk treatment increased the relative abundance of butyrate producing bacteria in mouse intestine, in addition to increasing Lachnospiraceae ucg-001, Lachnospiraceae ucg-008, and Ruminiclostridium 5 (Clostridium clusters xiva and IV), and decreased the relative abundance of bacterial Proteus that can promote inflammation. Clostridium clusters xiva and IV can decompose nondigestible oligosaccharides to produce acetic acid, propionic acid, and butyric acid. These organisms are usually close to host epithelial cells, which have a great impact on the host immune balance [92][93]. In a study of mice intestinal microorganisms, Clostridium clusters xiva and IV can help induce the accumulation and differentiation of Foxp3 + Treg cells in mouse colon. Clostridium can induce colon epithelial cells to release active TGF- β and other Treg inducing factors, which can induce Treg differentiation by regulating CD103+ DC. In addition, Clostridium has also been shown to induce IL-10 expressing Treg cells in the colon. Increasing the colonization of intestinal Clostridium can increase the body's resistance to allergy ^[94]. These microbes disappeared in the intestines of mice fed pasteurized milk. However, after the addition of ALP to

pasteurized milk, the changes in the intestinal probiotic microbiota observed in the raw milk treatment group reappeared and reduced allergic reactions ^[95].

6. Other Diseases

ALP supplementation has a probiotic effect on multiple organs of the body, including the treatment of intestinal-, liver-, and kidney-related diseases [96][97]. ALP supplementation can detoxify a variety of proinflammatory mediators in the intestinal cavity. Among them, ALP has the most significant detoxification function on LPS (also known as endotoxin). In recent years, LPS has been proved to be one of the key mediators connecting the development of intestinal and liver diseases and many other systemic diseases. LPS consists of core polysaccharide, O-antigen, and lipid A. ALP can remove the phosphate group on LPS lipid A by dephosphorylation, so as to relieve the toxicity of LPS [98][99][100]. In a study of liver inflammation, it was found that LPS induced chronic inflammation by stimulating the expression of TLR4 in tissue cells [101][102]. When the IAP gene was knocked out, the tolerance of mouse intestinal environment to LPS decreased significantly and was more vulnerable to intestinal validation [41] ^[63]. When intestinal injury occurs, LPS is more likely to enter the blood, causing liver injury and even serious diseases. When disease occurs, IAP supplementation—whether oral or injection—has been widely used to prevent and treat inflammatory diseases. For example, oral administration of recombinant ALP can prevent alcohol-induced hepatic steatosis and chronic liver failure [103][104]. Although IAP may be partially degraded in the stomach, oral administration after mixing IAP in drinking water is a very simple route of administration. A large number of experiments have proved that oral ALP supplementation can effectively increase the concentration of IAP in the intestinal cavity [69][78]. At the same time, after IAP supplementation in drinking water, the concentration of serum LPS in intestinal vena cava and portal vein decreased significantly, which will greatly reduce the harm of LPS translocation to the liver, so as to further protect the liver and reduce the development of malignant inflammatory circulation and liver fibrosis [105]. In human clinical studies, duodenal and enteral IAP was administered to patients with severe ulcerative colitis for 7 days, and no human safety problems, adverse events, or side effects of ALP were reported [106].

With regard to intestinal flora, it was found that the number of intestinal bacteria in IAP-ko mice decreased overall and that oral supplementation of IAP in WT mice could quickly restore the normal intestinal flora of mice affected by antibiotics ^[69]. IAP prevents HFD-induced metabolic endotoxemia by regulating intestinal flora ^[63]. In a zebrafish model, zebrafish lacking IAP are highly sensitive to LPS toxicity. IAP plays a crucial role in promoting mucosal tolerance to intestinal resident bacteria ^[98]. Knockout of the intestinal ALP gene (AKP3) in mice leads to metabolic abnormalities, resulting in visceral fat accumulation and hepatic steatosis ^[107]. On the other hand, an investigation found that the endogenous IAP level of rats decreased with age and that metabolic syndrome was common in older animals ^{[108][109]}. This suggests that "IAP deficiency" may be an inducement leading to metabolic syndrome and that the oral supplementary IAP dose can be easily adjusted to achieve the purpose of preventing or treating metabolic syndrome ^[69].

Studies have demonstrated that the use of ALP in the treatment of sepsis-induced AKI is promising ^{[110][111][112]}. In the treatment of acute renal injury, high-dose ALP (75 U/kg + 25 U/kg/h intravenous injection) can significantly

increase serum ALP activity, making serum ALP about 5 times higher than baseline ^[113]. In a sheep model of sepsis, ALP can reduce inflammation and improve lung function without adverse reactions ^[8]. Intravenous ALP is preferentially delivered to blood and to liver, kidney, and other abdominal organs at a lower dose. Therefore, in the treatment of renal injury, a high concentration of serum ALP level is required to increase the grade of renal tissue ^[114]. In addition, rodent model studies of isolated renal ischemia-reperfusion injury have shown that ALP treatment can reduce renal tubular injury ^[115].

For women at high risk of pregnancy complications due to LPS infection, the use of supplementary AP isozymes may be an attractive treatment option ^[116]. In a mouse model study, IAP inhibited LPS to play an inflammatory role by upregulating the expression of autophagy-related genes (ATG5, ATG16, IRGM1, TLR4) in the mouse small intestine. Oral ALP can prevent the immune stimulation of LPS in blood to the liver. ALP can remove the phosphate group on LPS and eliminate the toxicity of LPS. At the same time, ALP can reduce TLR4, TNF-a, matured IL-1 β , and NF- κ B expression by upregulating the level of mir146a in mouse liver tissue, which in turn reduces the inflammatory response of the liver ^[117]. It was found that endogenous IAP decreased during liver fibrosis, resulting in intestinal barrier dysfunction and fibrosis deterioration. Oral IAP can protect the intestinal barrier and further prevent the development of liver fibrosis through a TLR4-mediated mechanism ^[107]. Although the mechanism is unclear, oral and intravenous ALP play a renal protective role in various sepsis animal models ^{[8][105][118][119]}.

Animal	Treatment Method	Treatment Dosage	Treatment Frequency	Duration	Disease	Description	Reference
Rats	Oral	Base formula	Feed	4 days	NEC	Protect intestine	[<u>120]</u>
Rats	Oral	0.4, 4,or 40 U/kg	Feed	3 days	NEC	Preserving the intestinal epithelial barrier function	[<u>121]</u>
Rats	Oral	0.4, 4, or 40 U/kg	Feed	1 day	NEC	Decreased nitrosative stress; decreased intestinal TNF-α mRNA expression; decreased LSP translocation into the serum	[<u>122]</u>
Rats	Oral	0.4, 4, or 40 U/kg	Feed	1 day	NEC	Reduces systemic proinflammatory cytokine expression	[<u>123]</u>
Rats	Oral	700 U/kg	Gastroesophageal catheter	6 days	IBD	Protection against bacterial	[22]

Table 1. Preventive and therapeutic effects of alkaline phosphatase (ALP) on diseases.

Animal	Treatment Method	Treatment Dosage	Treatment Frequency	Duration	Disease	Description	Reference
						translocation	
Rats	Oral	1035 U	Drinking water	8 days	IBD	Reduced mRNA levels for TNF-α, IL-1β, IL-6, and iNOS	[<u>18</u>]
Mice	Oral	200 U/kg	Gavage	4 h	Liver injury	Reducing LPS toxicity and preventing liver injury	[<u>117]</u>
Mice	Oral	6 U/ml	Gavage	8 days	Food allergic	Reduction in CD103+CD11b+ dendritic cells and TGF-β-producing regulatory T cells in the mesenteric lymph nodes	[<u>91</u>]
Mice	Oral	6 U/ml	Gavage	8 days	Food allergic	Regulation of intestinal microbial community structure	[<u>95</u>]
Mice	Oral	100 or 300 U	Gavage	2 weeks	Chronic colitis	Inhibit the activation of intestinal epithelial cells and peritoneal macrophages and attenuate chronic murine colitis	[<u>124]</u>
Mice	Oral	100 U/mL	Drinking water	21 days	Metabolic syndrome	Alterations in the composition of the gut microbiota	[125]
Mice	Oral	150 or 300 U/mL	Drinking water	48 h	Gut barrier dysfunction	Decreased expression of intestinal junctional proteins and impaired barrier function	[<u>126]</u>
Mice	Oral	200 U/mL	Drinking water	5 days	Bacterial infections	Protected mice from antibiotic- associated	[<u>127]</u>

Animal	Treatment Method	Treatment Dosage	Treatment Frequency	Duration	Disease	Description	Reference
						bacterial infections	
Mice	Oral	100 U/mL	Drinking water	11 weeks	Metabolic syndrome	Inhibits absorption of endotoxin with dietary fat; prevents or reverses metabolic syndrome	[<u>63</u>]
Mice	Oral	300 U/mL	Drinking water	7 days	Inflammatory bowel diseases	Tissue myeloperoxidase activity and proinflammatory cytokines were significantly decreased	[<u>41</u>]
Mice	Oral	200 U/mL	Drinking water	4 days	Liver fibrosis	Protects the gut barrier and development of liver fibrosis via a TLR4-mediated mechanism	[105]
Mice	Oral	100 U/mL	Drinking water	Lifetime	Aging	Targeting crucial intestinal alterations, including gut barrier dysfunction, microbiome dysbiosis, and endotoxemia	[<u>78</u>]
Mice	Oral	200 U/mL	Liquid diet	10 days	Hepatosteatosis	Ameliorated the activation of hepatic stellate cells and prevented their lipogenic effect on hepatocytes	[<u>105</u>]
Human	Oral	30,000 U	Infusion pump	7 days	Ulcerative colitis	Decrease the C- reactive protein and stool calprotectin levels	[<u>106]</u>

Animal	Treatment Method	Treatment Dosage	Treatment Frequency	Duration	Disease	Description	Reference
Rats	Injection	1000 U/kg	Intraperitoneal	4 days	Acute liver failure	Reduced LPS activity and hepatic TLR4 expression	[<u>104]</u>
Rats	Injection	1000 U/kg	Intraperitoneal	24 h	Acute kidney injury	Reduce renal inflammation; dephosphorylation of ATP and LPS	[<u>118]</u>
Rats	Injection	500 U/kg	Intraperitoneal	5 min	Partial liver resection	Attenuate both hepatic and pulmonary injury	[<u>128]</u>
Mice	Injection	100 U/mL	Intestinal loop	2 h	Intestinal flora disorder	Inhibiting the concentration of luminal nucleotide triphosphates	[<u>129</u>]
Mice	Injection	15 U/mL	Intravenous	1 day	Sepsis	Normalize body temperature	[<u>130</u>]
Mice	Injection	150 U	Intravenous	5 min	Pregnancy complications	Protects early pregnancy defects	[<u>116</u>]
Mice	Injection	150 U/kg	Intravenous	72 h	Secondary peritonitis	Attenuates the inflammatory response both locally and systemically and reduces associated liver and lung damage	[<u>131</u>]
Human	Injection	5.6 U/kg/h	Intravenous	36 h	Cardiac surgery	Endogenous alkaline phosphatase release	[<u>132]</u>
Human	Injection	67.5 U/kg + 132.5 U/kg/24 h	Intravenous	48 h	Acute kidney injury	Reductions in the systemic markers C-reactive protein, IL-6, and LPS- binding protein and in the urinary excretion of kidney injury molecule-1 and IL-18	[<u>111</u>]

Animal	Treatment Method	Treatment Dosage	Treatment Frequency	Duration	Disease	Description	Reference
Piglet	Injection	1, 5, or 25 U/kg/h	Intravenous	4 h	Acute kidney injury	Increased serum or renal tissue AP activity	[<u>113]</u>
Piglet	Injection	1, 5, or 25 U/kg/h	Intravenous	4 h	Cardiac surgery	Increased kidney and liver tissue alkaline phosphatase activity	[<u>133]</u>

References

- 1. Millán, J.L. Alkaline phosphatases. Purinergic Signal. 2006, 2, 335–341.
- 2. Yang, Y.; Rader, E.; Peters-Carr, M.; Bent, R.C.; Smilowitz, J.T.; Guillemin, K.; Rader, B. Ontogeny of alkaline phosphatase activity in infant intestines and breast milk. BMC Pediatrics 2019, 19, 1–7.
- 3. Miller, P.D. Bone disease in CKD: A focus on osteoporosis diagnosis and management. Am. J. Kidney Dis. 2014, 64, 290–304.
- Le Bricon, T.; Gay-Bellile, C.; Cottu, P.; Benlakehal, M.; Guillon, H.; Houzé, P. Lectin affinity electrophoresis of serum alkaline phosphatase in metastasized breast cancer. J. Clin. Lab. Anal. 2010, 24, 20–24.
- Lassenius, M.I.; Fogarty, C.L.; Blaut, M.; Haimila, K.; Riittinen, L.; Paju, A.; Kirveskari, J.; Järvelä, J.; Ahola, A.J.; Gordin, D.; et al. Intestinal alkaline phosphatase at the crossroad of intestinal health and disease—A putative role in type 1 diabetes. J. Intern. Med. 2017, 281, 586–600.
- 6. Siddique, A.; Kowdley, K.V. Approach to a Patient with Elevated Serum Alkaline Phosphatase. Clin. Liver Dis. 2012, 16, 199–229.
- Neumann, F.; Kubuschok, B.; Ertan, K.; Schormann, C.; Stevanovic, S.; Preuss, K.D.; Schmidt, W.; Pfreundschuh, M. A peptide epitope derived from the cancer testis antigen HOM-MEL-40/SSX2 capable of inducing CD4+ and CD8+ T-cell as well as B-cell responses. Cancer Immunol. Immunother. 2011, 60, 1333–1346.
- 8. Hümmeke-Oppers, F.; Hemelaar, P.; Pickkers, P. Innovative drugs to target renal inflammation in sepsis: Alkaline phosphatase. Front. Pharmacol. 2019, 10, 919.
- 9. Ooi, K.; Shiraki, K.; Morishita, Y.; Nobori, T. High-molecular intestinal alkaline phosphatase in chronic liver diseases. J. Clin. Lab. Anal. 2007, 21, 133–139.
- Bensouda, Y.; Kaikani, W.; Ahbeddou, N.; Rahhali, R.; Jabri, M.; Mrabti, H.; Boussen, H.; Errihani,
 H. Treatment for metastatic nasopharyngeal carcinoma. Eur. Ann. Otorhinolaryngol. Head Neck

Dis. 2011, 128, 79-85.

- 11. World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment; World Health Organization: Geneva, Switzerland, 1979; ISBN 9241700483.
- Eisenhauer, E.A.; Therasse, P.; Bogaerts, J.; Schwartz, L.H.; Sargent, D.; Ford, R.; Dancey, J.; Arbuck, S.; Gwyther, S.; Mooney, M.; et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur. J. Cancer 2009, 45, 228–247.
- Jin, Y.; Yuan, M.Q.; Chen, J.Q.; Zhang, Y.P. Serum alkaline phosphatase predicts survival outcomes in patients with skeletal metastatic nasopharyngeal carcinoma. Clinics 2015, 70, 264– 272.
- 14. Muginova, S.V.; Zhavoronkova, A.M.; Polyakov, A.E.; Shekhovtsova, T.N. Application of alkaline phosphatases from different sources in pharmaceutical and clinical analysis for the determination of their cofactors; zinc and magnesium ions. Anal. Sci. 2007, 23, 357–363.
- 15. Metwalli, O.M.; Mourand, F.E. Studies on organ-specific alkaline phosphatases in relation to its diagnostic value. Z. Ernährungswissenschaft 1980, 19, 154–158.
- Narisawa, S.; Huang, L.; Iwasaki, A.; Hasegawa, H.; Alpers, D.H.; Millán, J.L. Accelerated Fat Absorption in Intestinal Alkaline Phosphatase Knockout Mice. Mol. Cell. Biol. 2003, 23, 7525– 7530.
- 17. Molnár, K.; Vannay, Á.; Szebeni, B.; Bánki, N.F.; Sziksz, E.; Cseh, Á.; Gyorffy, H.; Lakatos, P.L.; Papp, M.; Arató, A.; et al. Intestinal alkaline phosphatase in the colonic mucosa of children with inflammatory bowel disease. World J. Gastroenterol. 2012, 18, 3254–3259.
- 18. Tuin, A.; Poelstra, K.; De Jager-Krikken, A.; Bok, L.; Raaben, W.; Velders, M.P.; Dijkstra, G. Role of alkaline phosphatase in colitis in man and rats. Gut 2009, 58, 379–387.
- Akiba, Y.; Mizumori, M.; Guth, P.H.; Engel, E.; Kaunitz, J.D. Duodenal brush border intestinal alkaline phosphatase activity affects bicarbonate secretion in rats. Am. J. Physiol.-Gastrointest. Liver Physiol. 2007, 293, G1223–G1233.
- 20. McConnell, R.E.; Higginbotham, J.N.; Shifrin, D.A.; Tabb, D.L.; Coffey, R.J.; Tyska, M.J. The enterocyte microvillus is a vesicle-generating organelle. J. Cell Biol. 2009, 185, 1285–1298.
- 21. Bayer, P.M.; Hotschek, H.; Knoth, E. Intestinal alkaline phosphatase and the abo blood group system—A new aspect. Clin. Chim. Acta 1980, 108, 81–87.
- Martínez-Moya, P.; Ortega-González, M.; González, R.; Anzola, A.; Ocón, B.; Hernández-Chirlaque, C.; López-Posadas, R.; Suárez, M.D.; Zarzuelo, A.; Martínez-Augustin, O.; et al. Exogenous alkaline phosphatase treatment complements endogenous enzyme protection in colonic inflammation and reduces bacterial translocation in rats. Pharmacol. Res. 2012, 66, 144– 153.

- 23. Goldberg, R.F.; Austen, W.G.; Zhang, X.; Munene, G.; Mostafa, G.; Biswas, S.; McCormack, M.; Eberlin, K.R.; Nguyen, J.T.; Tatlidede, H.S.; et al. Intestinal alkaline phosphatase is a gut mucosal defense factor maintained by enteral nutrition. Proc. Natl. Acad. Sci. USA 2008, 105, 3551–3556.
- Chen, K.T.; Malo, M.S.; Beasley-Topliffe, L.K.; Poelstra, K.; Millan, J.L.; Mostafa, G.; Alam, S.N.; Ramasamy, S.; Warren, H.S.; Hohmann, E.L.; et al. A role for intestinal alkaline phosphatase in the maintenance of local gut immunity. Dig. Dis. Sci. 2011, 56, 1020–1027.
- 25. Kaliannan, K.; Wang, B.; Li, X.Y.; Kim, K.J.; Kang, J.X. A host-microbiome interaction mediates the opposing effects of omega-6 and omega-3 fatty acids on metabolic endotoxemia. Sci. Rep. 2015, 5, 11276.
- Montagne, L.; Toullec, R.; Savidge, T.; Lallès, J.P. Morphology and enzyme activities of the small intestine are modulated by dietary protein source in the preruminant calf. Reprod. Nutr. Dev. 1999, 39, 455–466.
- 27. Boudry, G.; Lallès, J.P.; Malbert, C.H.; Bobillier, E.; Sève, B. Diet-related adaptation of the small intestine at weaning in pigs is functional rather than structural. J. Pediatric Gastroenterol. Nutr. 2002, 34, 180–187.
- 28. Lallès, J.P. Intestinal alkaline phosphatase: Multiple biological roles in maintenance of intestinal homeostasis and modulation by diet. Nutr. Rev. 2010, 68, 323–332.
- Okazaki, Y.; Katayama, T. Glucomannan consumption elevates colonic alkaline phosphatase activity by up-regulating the expression of IAP-1, which is associated with increased production of protective factors for gut epithelial homeostasis in high-fat diet–fed rats. Nutr. Res. 2017, 43, 43– 50.
- 30. Okazaki, Y.; Katayama, T. Consumption of non-digestible oligosaccharides elevates colonic alkaline phosphatase activity by up-regulating the expression of IAP-I, with increased mucins and microbial fermentation in rats fed a high-fat diet. Br. J. Nutr. 2019, 121, 146–154.
- Nakaoka, K.; Yamada, A.; Noda, S.; Goseki-Sone, M. Vitamin D-restricted high-fat diet downregulates expression of intestinal alkaline phosphatase isozymes in ovariectomized rats. Nutr. Res. 2018, 53, 23–31.
- 32. Prakash, U.N.S.; Srinivasan, K. Beneficial influence of dietary spices on the ultrastructure and fluidity of the intestinal brush border in rats. Br. J. Nutr. 2010, 104, 31–39.
- Narisawa, S.; Hoylaerts, M.F.; Doctor, K.S.; Fukuda, M.N.; Alpers, D.H.; Millán, J.L. A novel phosphatase upregulated in Akp3 knockout mice. Am. J. Physiol.-Gastrointest. Liver Physiol. 2007, 293, G1068–G1077.
- 34. Clark, S.B.; Holt, P.R. Rate-limiting steps in steady-state intestinal absorption of trioctanoin-1-14C. Effect of biliary and pancreatic flow diversion. J. Clin. Investig. 1968, 47, 612–623.

- Alpers, D.H.; Zhang, Y.; Ahnen, D.J. Synthesis and parallel secretion of rat intestinal alkaline phosphatase and a surfactant-like particle protein. Am. J. Physiol.-Endocrinol. Metab. 1995, 268, E1205–E1214.
- 36. de La Serre, C.B.; Ellis, C.L.; Lee, J.; Hartman, A.L.; Rutledge, J.C.; Raybould, H.E. Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. Am. J. Physiol.-Gastrointest. Liver Physiol. 2010, 299, G440–G448.
- 37. Ghosh, S.; DeCoffe, D.; Brown, K.; Rajendiran, E.; Estaki, M.; Dai, C.; Yip, A.; Gibson, D.L. Fish Oil Attenuates Omega-6 Polyunsaturated Fatty Acid-Induced Dysbiosis and Infectious Colitis but Impairs LPS Dephosphorylation Activity Causing Sepsis. PLoS ONE 2013, 8, e55468.
- 38. Montoya, C.A.; Leterme, P.; Lalles, J.P. A protein-free diet alters small intestinal architecture and digestive enzyme activities in rats. Reprod. Nutr. Dev. 2006, 46, 49–56.
- 39. Szebeni, B.; Veres, G.; Dezsőfi, A.; Rusai, K.; Vannay, Á.; Mraz, M.; Majorova, E.; Arató, A. Increased expression of Toll-like receptor (TLR) 2 and TLR4 in the colonic mucosa of children with inflammatory bowel disease. Clin. Exp. Immunol. 2008, 151, 34–41.
- 40. Andoh, A.; Fujiyama, Y. Therapeutic approaches targeting intestinal microflora in inflammatory bowel disease. World J. Gastroenterol. 2006, 12, 4452–4460.
- 41. Ramasamy, S.; Nguyen, D.D.; Eston, M.A.; Nasrin Alam, S.; Moss, A.K.; Ebrahimi, F.; Biswas, B.; Mostafa, G.; Chen, K.T.; Kaliannan, K.; et al. Intestinal alkaline phosphatase has beneficial effects in mouse models of chronic colitis. Inflamm. Bowel Dis. 2011, 17, 532–542.
- Bol-Schoenmakers, M.; Fiechter, D.; Raaben, W.; Hassing, I.; Bleumink, R.; Kruijswijk, D.; Maijoor, K.; Tersteeg-Zijderveld, M.; Brands, R.; Pieters, R. Intestinal alkaline phosphatase contributes to the reduction of severe intestinal epithelial damage. Eur. J. Pharmacol. 2010, 633, 71–77.
- 43. Kaplan, J.L.; Shi, H.N.; Walker, W.A. The role of microbes in developmental immunologic programming. Pediatric Res. 2011, 69, 465–472.
- 44. Artis, D. Epithelial-cell recognition of commensal bacteria and maintenance of immune homeostasis in the gut. Nat. Rev. Immunol. 2008, 8, 411–420.
- 45. Round, J.L.; Mazmanian, S.K. The gut microbiota shapes intestinal immune responses during health and disease. Nat. Rev. Immunol. 2009, 9, 313–323.
- 46. Walker, W.A. The importance of appropriate initial bacterial colonization of the intestine in newborn, child, and adult health. Pediatric Res. 2017, 82, 387–395.
- Guarner, F.; Bourdet-Sicard, R.; Brandtzaeg, P.; Gill, H.S.; McGuirk, P.; van Eden, W.; Versalovic, J.; Weinstock, J.V.; Rook, G.A.W. Mechanisms of disease: The hygiene hypothesis revisited. Nat. Clin. Pract. Gastroenterol. Hepatol. 2006, 3, 275–284.

- 48. Martin, C.R.; Walker, W.A. Innate and mucosal immunity in the developing gastrointestinal tract: Relationship to early and later disease. In Avery's Diseases of the Newborn; Elsevier: Amsterdam, The Netherlands, 2012; pp. 994–1006.
- 49. Claud, E.C.; Lu, L.; Anton, P.M.; Savidge, T.; Walker, W.A.; Cherayil, B.J. Developmentally regulated IkB expression in intestinal epithelium and susceptibility to flagellin-induced inflammation. Proc. Natl. Acad. Sci. USA 2004, 101, 7404–7408.
- Nanthakumar, N.; Meng, D.; Goldstein, A.M.; Zhu, W.; Lu, L.; Uauy, R.; Llanos, A.; Claud, E.C.; Walker, W.A. The mechanism of excessive intestinal inflammation in necrotizing enterocolitis: An immature innate immune response. PLoS ONE 2011, 6, e17776.
- Groer, M.W.; Gregory, K.E.; Louis-Jacques, A.; Thibeau, S.; Walker, W.A. The very low birth weight infant microbiome and childhood health. Birth Defects Res. Part C Embryo Today Rev. 2015, 105, 252–264.
- 52. McGuire, W.; Anthony, M.Y. Donor human milk versus formula for preventing necrotising enterocolitis in preterm infants: Systematic review. Arch. Dis. Child.-Fetal Neonatal Ed. 2003, 88, 11–14.
- 53. Lucas, A.; Cole, T.J. Breast milk and neonatal necrotising enterocolitis. Lancet 1990, 336, 1519– 1523.
- 54. Moreira, A.P.B.; Texeira, T.F.S.; Ferreira, A.B.; Do Carmo Gouveia Peluzio, M.; De Cássia Gonçalves Alfenas, R. Influence of a high-fat diet on gut microbiota, intestinal permeability and metabolic endotoxaemia. Br. J. Nutr. 2012, 108, 801–809.
- 55. Repa, A.; Thanhaeuser, M.; Endress, D.; Weber, M.; Kreissl, A.; Binder, C.; Berger, A.; Haiden, N. Probiotics (Lactobacillus acidophilus and Bifidobacterium bifidum) prevent NEC in VLBW infants fed breast milk but not formula. Pediatric Res. 2015, 77, 381–388.
- Underwood, M.A.; Gaerlan, S.; De Leoz, M.L.A.; Dimapasoc, L.; Kalanetra, K.M.; Lemay, D.G.; German, J.B.; Mills, D.A.; Lebrilla, C.B. Human milk oligosaccharides in premature infants: Absorption, excretion, and influence on the intestinal microbiota. Pediatric Res. 2015, 78, 670– 677.
- 57. Musilova, S.; Rada, V.; Vlkova, E.; Bunesova, V. Beneficial effects of human milk oligosaccharides on gut microbiota. Benef. Microbes 2014, 5, 273–283.
- Hunt, K.M.; Foster, J.A.; Forney, L.J.; Schütte, U.M.E.; Beck, D.L.; Abdo, Z.; Fox, L.K.; Williams, J.E.; McGuire, M.K.; McGuire, M.A. Characterization of the diversity and temporal stability of bacterial communities in human milk. PLoS ONE 2011, 6, e21313.
- Bridgman, S.L.; Konya, T.; Azad, M.B.; Sears, M.R.; Becker, A.B.; Turvey, S.E.; Mandhane, P.J.; Subbarao, P.; Allen, R.; Anand, S.S.; et al. Infant gut immunity: A preliminary study of IgA associations with breastfeeding. J. Dev. Orig. Health Dis. 2016, 7, 68–72.

- 60. Gregory, K.E.; Walker, W.A. Immunologic Factors in Human Milk and Disease Prevention in the Preterm Infant. Curr. Pediatrics Rep. 2013, 1, 222–228.
- 61. Lallès, J.P. Intestinal alkaline phosphatase: Novel functions and protective effects. Nutr. Rev. 2014, 72, 82–94.
- 62. Estaki, M.; DeCoffe, D.; Gibson, D.L. Interplay between intestinal alkaline phosphatase, diet, gut microbes and immunity. World J. Gastroenterol. 2014, 20, 15650–15656.
- Kaliannan, K.; Hamarneh, S.R.; Economopoulos, K.P.; Alam, S.N.; Moaven, O.; Patel, P.; Malo, N.S.; Ray, M.; Abtahi, S.M.; Muhammad, N.; et al. Intestinal alkaline phosphatase prevents metabolic syndrome in mice. Proc. Natl. Acad. Sci. USA 2013, 110, 7003–7008.
- 64. Millán, J.L. Mammalian Alkaline Phosphatases: From Biology to Applications in Medicine and Biotechnology; John Wiley & Sons: Hoboken, NJ, USA, 2006; ISBN 3527607471.
- Biesterveld, B.E.; Koehler, S.M.; Heinzerling, N.P.; Rentea, R.M.; Fredrich, K.; Welak, S.R.; Gourlay, D.M. Intestinal alkaline phosphatase to treat necrotizing enterocolitis. J. Surg. Res. 2015, 196, 235–240.
- Heinzerling, N.P.; Liedel, J.L.; Welak, S.R.; Fredrich, K.; Biesterveld, B.E.; Pritchard, K.A.; Gourlay, D.M. Intestinal alkaline phosphatase is protective to the preterm rat pup intestine. J. Pediatric Surg. 2014, 49, 954–960.
- Chen, K.T.; Malo, M.S.; Moss, A.K.; Zeller, S.; Johnson, P.; Ebrahimi, F.; Mostafa, G.; Alam, S.N.; Ramasamy, S.; Warren, H.S.; et al. Identification of specific targets for the gut mucosal defense factor intestinal alkaline phosphatase. Am. J. Physiol.-Gastrointest. Liver Physiol. 2010, 299, G467–G475.
- Liu, W.; Hu, D.; Huo, H.; Zhang, W.; Adiliaghdam, F.; Morrison, S.; Ramirez, J.M.; Gul, S.S.; Hamarneh, S.R.; Hodin, R.A. Intestinal alkaline phosphatase regulates tight junction protein levels. J. Am. Coll. Surg. 2015, 222, 1009–1017.
- 69. Malo, M.S.; Nasrin Alam, S.; Mostafa, G.; Zeller, S.J.; Johnson, P.V.; Mohammad, N.; Chen, K.T.; Moss, A.K.; Ramasamy, S.; Faruqui, A.; et al. Intestinal alkaline phosphatase preserves the normal homeostasis of gut microbiota. Gut 2010, 59, 1476–1484.
- Detel, D.; Baticic, L.; Varljen, J. The influence of age on intestinal dipeptidyl peptidase IV (DPP IV/CD26), disaccharidases, and alkaline phosphatase enzyme activity in C57BL/6 mice. Exp. Aging Res. 2008, 34, 49–62.
- Rentea, R.M.; Rentea, M.J.; Biesterveld, B.; Liedel, J.L.; Gourlay, D.M. Factors Known to Influence the Development of Necrotizing Enterocolitis to Modify Expression and Activity of Intestinal Alkaline Phosphatase in a Newborn Neonatal Rat Model. Eur. J. Pediatric Surg. 2019, 29, 290–297.

- 72. Neu, J. Mother's Own Milk: How Does It Differ from Donor Milk for the Baby. Breastfeed. Med. 2019, 14, S3–S4.
- Chatterton, D.E.W.; Nguyen, D.N.; Bering, S.B.; Sangild, P.T. Anti-inflammatory mechanisms of bioactive milk proteins in the intestine of newborns. Int. J. Biochem. Cell Biol. 2013, 45, 1730– 1747.
- 74. Morais, J.; Faria, A.; Teixeira, D.; Barreiros-mota, I.; Dur, C.; Brito, S.; Cardoso, M.; Macedo, I.; Pereira, E.; Tom, T. Influence of Human Milk on Very Preterms' Gut Microbiota and Alkaline Phosphatase Activity. Nutrients 2021, 13, 1564.
- 75. Fawley, J.; Koehler, S.; Cabrera, S.; Lam, V.; Fredrich, K.; Hessner, M.; Salzman, N.; Gourlay, D. Intestinal alkaline phosphatase deficiency leads to dysbiosis and bacterial translocation in the newborn intestine. J. Surg. Res. 2017, 218, 35–42.
- 76. Mehta, N.N.; McGillicuddy, F.C.; Anderson, P.D.; Hinkle, C.C.; Shah, R.; Pruscino, L.; Tabita-Martinez, J.; Sellers, K.F.; Rickels, M.R.; Reilly, M.P. Experimental endotoxemia induces adipose inflammation and insulin resistance in humans. Diabetes 2010, 59, 172–181.
- 77. Hava, G.; Vered, L.; Yael, M.; Mordechai, H.; Mahoud, H. Alterations in behavior in adult offspring mice following maternal inflammation during pregnancy. Dev. Psychobiol. 2006, 48, 162–168.
- 78. Kühn, F.; Adiliaghdam, F.; Cavallaro, P.M.; Hamarneh, S.R.; Tsurumi, A.; Hoda, R.S.; Munoz, A.R.; Dhole, Y.; Ramirez, J.M.; Liu, E.; et al. Intestinal alkaline phosphatase targets the gut barrier to prevent aging. JCI Insight 2020, 5, e134049.
- 79. Furlan Freguia, C.; Marriott, A.; Gill, D.; Kaleko, M. Maternal treatment with oral intestinal alkaline phosphatase mitigates high fat diet-induced cognitive disorders in offspring mice. Behav. Brain Res. 2020, 392, 112701.
- Bjelaković, L.; Kocić, G.; Cvetković, T.; Stojanović, D.; Najmen, S.; Jevtovic, T.; Pop-Trajković, Z. Arginase activity in human milk during the first month of lactation. J. Basic Clin. Physiol. Pharmacol. 2010, 21, 187–200.
- 81. Terho, E.O.; Helenius, H.; Koskenvuo, M. Farm environment in childhood prevents the development of allergies. Clin. Exp. Allergy 2000, 30, 201–208.
- Alfvén, T.; Braun-Fahrländer, C.; Brunekreef, B.; Von Mutius, E.; Riedler, J.; Scheynius, A.; Van Hage, M.; Wickman, M.; Benz, M.R.; Budde, J.; et al. Allergic diseases and atopic sensitization in children related to farming and anthroposophic lifestyle—The PARSIFAL study. Allergy 2006, 61, 414–421.
- 83. Von Mutius, E.; Vercelli, D. Farm living: Effects on childhood asthma and allergy. Nat. Rev. Immunol. 2010, 10, 861–868.

- Waser, M.; Michels, K.B.; Bieli, C.; Flöistrup, H.; Pershagen, G.; Von Mutius, E.; Ege, M.; Riedler, J.; Schram-Bijkerk, D.; Brunekreef, B.; et al. Inverse association of farm milk consumption with asthma and allergy in rural and suburban populations across Europe. Clin. Exp. Allergy 2007, 37, 661–670.
- 85. Ege, M.J.; Frei, R.; Bieli, C.; Schram-Bijkerk, D.; Waser, M.; Benz, M.R.; Weiss, G.; Nyberg, F.; van Hage, M.; Pershagen, G.; et al. Not all farming environments protect against the development of asthma and wheeze in children. J. Allergy Clin. Immunol. 2007, 119, 1140–1147.
- 86. Perkin, M.R.; Strachan, D.P. Which aspects of the farming lifestyle explain the inverse association with childhood allergy? J. Allergy Clin. Immunol. 2006, 117, 1374–1381.
- Loss, G.; Apprich, S.; Waser, M.; Kneifel, W.; Genuneit, J.; Büchele, G.; Weber, J.; Sozanska, B.; Danielewicz, H.; Horak, E.; et al. The Protective Effect of Farm Milk Consumption on Childhood Asthma and Atopy: The GABRIELA Study. Available online: https://www.sciencedirect.com/science/article/pii/S0091674911012346?via%3Dihub (accessed on 11 November 2020).
- Riedler, J.; Braun-Fahrländer, C.; Eder, W.; Schreuer, M.; Waser, M.; Maisch, S.; Carr, D.; Schierl, R.; Nowak, D.; Von Mutius, E. Exposure to farming in early life and development of asthma and allergy: A cross-sectional survey. Lancet 2001, 358, 1129–1133.
- 89. Abbring, S.; Verheijden, K.A.T.; Diks, M.A.P.; Leusink-Muis, A.; Hols, G.; Baars, T.; Garssen, J.; van Esch, B.C.A.M. Raw cow's milk prevents the development of airway inflammation in a murine house dust mite-induced asthma model. Front. Immunol. 2017, 8, 1045.
- Abbring, S.; Wolf, J.; Ayechu-muruzabal, V.; Diks, M.A.P.; Alhamwe, B.A.; Alhamdan, F.; Harb, H.; Renz, H.; Garn, H.; Garssen, J.; et al. Raw cow's milk reduces allergic symptoms in a murine model for food allergy—A potential role for epigenetic modifications. Nutrients 2019, 11, 1721.
- 91. Abbring, S.; Ryan, J.T.; Diks, M.A.P.; Hols, G.; Garssen, J.; Van Esch, B.C.A.M. Suppression of food allergic symptoms by raw Cow's milk in mice is retained after skimming but abolished after heating the milk—A promising contribution of alkaline phosphatase. Nutrients 2019, 11, 1499.
- 92. Nagano, Y.; Itoh, K.; Honda, K. The induction of Treg cells by gut-indigenous Clostridium. Curr. Opin. Immunol. 2012, 24, 392–397.
- 93. Lopetuso, L.R.; Scaldaferri, F.; Petito, V.; Gasbarrini, A. Commensal Clostridia: Leading players in the maintenance of gut homeostasis. Gut Pathog. 2013, 5, 23.
- Atarashi, K.; Tanoue, T.; Shima, T.; Imaoka, A.; Kuwahara, T.; Momose, Y.; Cheng, G.; Yamasaki, S.; Saito, T.; Ohba, Y.; et al. Induction of colonic regulatory T cells by indigenous Clostridium species. Science 2011, 331, 337–341.
- 95. Abbring, S.; Engen, P.A.; Naqib, A.; Green, S.J.; Garssen, J.; Keshavarzian, A.; van Esch,B.C.A.M. Raw milk-induced protection against food allergic symptoms in mice is accompanied by

shifts in microbial community structure. Int. J. Mol. Sci. 2021, 22, 3417.

- 96. Peters, E.; van Elsas, A.; Heemskerk, S.; Jonk, L.; van der Hoeven, J.; Arend, J.; Masereeuw, R.; Pickkers, P. Alkaline Phosphatase as a Treatment of Sepsis-Associated Acute Kidney Injury. J. Pharmacol. Exp. Ther. 2013, 344, 2–7.
- 97. Peters, E.; Masereeuw, R.; Pickkers, P. The potential of alkaline phosphatase as a treatment for sepsis-associated acute kidney injury. Nephron Clin. Pract. 2014, 127, 144–148.
- Bates, J.M.; Akerlund, J.; Mittge, E.; Guillemin, K. Intestinal Alkaline Phosphatase Detoxifies Lipopolysaccharide and Prevents Inflammation in Zebrafish in Response to the Gut Microbiota. Cell Host Microbe 2007, 2, 371–382.
- Poelstra, K.; Bakker, W.W.; Klok, P.A.; Kamps, J.A.A.M.; Hardonk, M.J.; Meijer, D.K.F.
 Dephosphorylation of endotoxin by alkaline phosphatase in vivo. Am. J. Pathol. 1997, 151, 1163– 1169.
- 100. Miller, S.I.; Ernst, R.K.; Bader, M.W. LPS, TLR4 and infectious disease diversity. Nat. Rev. Microbiol. 2005, 3, 36–46.
- 101. Vaure, C.; Liu, Y. A comparative review of toll-like receptor 4 expression and functionality in different animal species. Front. Immunol. 2014, 5, 316.
- 102. Pimentel-Nunes, P.; Soares, J.B.; Roncon-Albuquerque, R.; Dinis-Ribeiro, M.; Leite-Moreira, A.F. Toll-like receptors as therapeutic targets in gastrointestinal diseases. Expert Opin. Ther. Targets 2010, 14, 347–368.
- 103. Hamarneh, S.R.; Kim, B.M.; Kaliannan, K.; Morrison, S.A.; Tantillo, T.J.; Tao, Q.; Mohamed, M.M.R.; Ramirez, J.M.; Karas, A.; Liu, W.; et al. Intestinal Alkaline Phosphatase Attenuates Alcohol-Induced Hepatosteatosis in Mice. Dig. Dis. Sci. 2017, 62, 2021–2034.
- 104. Engelmann, C.; Adebayo, D.; Oria, M.; De Chiara, F.; Novelli, S.; Habtesion, A.; Davies, N.; Andreola, F.; Jalan, R. Recombinant Alkaline Phosphatase Prevents Acute on Chronic Liver Failure. Sci. Rep. 2020, 10, 389.
- 105. Liu, Y.; Cavallaro, P.M.; Kim, B.M.; Liu, T.; Wang, H.; Kühn, F.; Adiliaghdam, F.; Liu, E.; Vasan, R.; Samarbafzadeh, E.; et al. A role for intestinal alkaline phosphatase in preventing liver fibrosis. Theranostics 2020, 11, 14–26.
- 106. Lukas, M.; Drastich, P.; Konecny, M.; Gionchetti, P.; Urban, O.; Cantoni, F.; Bortlik, M.; Duricova, D.; Bulitta, M. Exogenous alkaline phosphatase for the treatment of patients with moderate to severe ulcerative colitis. Inflamm. Bowel Dis. 2010, 16, 1180–1186.
- 107. Nakano, T.; Inoue, I.; Koyama, I.; Kanazawa, K.; Nakamura, K.I.; Narisawa, S.; Tanaka, K.; Akita, M.; Masuyama, T.; Seo, M.; et al. Disruption of the murine intestinal alkaline phosphatase gene

Akp3 impairs lipid transcytosis and induces visceral fat accumulation and hepatic steatosis. Am. J. Physiol.-Gastrointest. Liver Physiol. 2007, 292, G1439–G1449.

- 108. Umegaki, H. Metabolic syndrome in the elderly. Jpn. J. Geriatr. 2008, 45, 251–258.
- 109. Jang, I.S.; Jung, K.K.; Cho, J.S. Influence of age on duodenal brush border membrane and specific activities of brush border membrane enzymes in wistar rats. Exp. Anim. 2000, 49, 281– 287.
- 110. Rezaeinasab, M.; Rad, M. Analytical survey of human rabies and animal bite prevalence during one decade in the province of Kerman, Iran. Crit. Care 2008, 12, P42.
- 111. Pickkers, P.; Heemskerk, S.; Schouten, J.; Laterre, P.F.; Vincent, J.L.; Beishuizen, A.; Jorens, P.G.; Spapen, H.; Bulitta, M.; Peters, W.H.M.; et al. Alkaline phosphatase for treatment of sepsisinduced acute kidney injury: A prospective randomized double-blind placebo-controlled trial. Crit. Care 2012, 16, R14.
- 112. Pickkers, P.; Mehta, R.L.; Murray, P.T.; Joannidis, M.; Molitoris, B.A.; Kellum, J.A.; Bachler, M.; Hoste, E.A.J.; Hoiting, O.; Krell, K.; et al. Effect of human recombinant alkaline phosphatase on 7day creatinine clearance in patients with sepsis-associated acute kidney injury a randomized clinical trial. JAMA 2018, 320, 1998–2009.
- 113. Davidson, J.A.; Khailova, L.; Treece, A.; Robison, J.; Soranno, D.E.; Jaggers, J.; Ing, R.J.; Lawson, S.; Lujan, S.O. Alkaline Phosphatase Treatment of Acute Kidney Injury in an Infant Piglet Model of Cardiopulmonary Bypass with Deep Hypothermic Circulatory Arrest. Sci. Rep. 2019, 9, 14175.
- 114. Peters, E.; Stevens, J.; Arend, J.; Guan, Z.; Raaben, W.; Laverman, P.; Van Elsas, A.; Masereeuw, R.; Pickkers, P. Biodistribution and translational pharmacokinetic modeling of a human recombinant alkaline phosphatase. Int. J. Pharm. 2015, 495, 122–131.
- 115. Peters, E.; Ergin, B.; Kandil, A.; Gurel-Gurevin, E.; van Elsas, A.; Masereeuw, R.; Pickkers, P.; Ince, C. Effects of a human recombinant alkaline phosphatase on renal hemodynamics, oxygenation and inflammation in two models of acute kidney injury. Toxicol. Appl. Pharmacol. 2016, 313, 88–96.
- 116. Lei, W.; Ni, H.; Herington, J.; Reese, J.; Paria, B.C. Alkaline phosphatase protects lipopolysaccharide-induced early pregnancy defects in mice. PLoS ONE 2015, 10, e0123243.
- 117. Wu, H.; Wang, Y.; Yao, Q.; Fan, L.; Meng, L.; Zheng, N.; Li, H.; Wang, J. Alkaline phosphatase attenuates LPS-induced liver injury by regulating the miR-146a-related inflammatory pathway. Int. Immunopharmacol. 2021, 101, 108149.
- 118. Peters, E.; Geraci, S.; Heemskerk, S.; Wilmer, M.J.; Bilos, A.; Kraenzlin, B.; Gretz, N.; Pickkers, P.; Masereeuw, R. Alkaline phosphatase protects against renal inflammation through

dephosphorylation of lipopolysaccharide and adenosine triphosphate. Br. J. Pharmacol. 2015, 172, 4932–4945.

- Heemskerk, S.; Masereeuw, R.; Moesker, O.; Bouw, M.P.W.J.M.; Van Der Hoeven, J.G.; Peters, W.H.M.; Russel, F.G.M.; Pickkers, P. Alkaline phosphatase treatment improves renal function in severe sepsis or septic shock patients. Crit. Care Med. 2009, 37, 417–423.
- Whitehouse, J.S.; Riggle, K.M.; Purpi, D.P.; Mayer, A.N.; Pritchard, K.A.; Oldham, K.T.; Gourlay, D.M. The protective role of intestinal alkaline phosphatase in necrotizing enterocolitis. J. Surg. Res. 2010, 163, 79–85.
- 121. Rentea, R.M.; Liedel, J.L.; Welak, S.R.; Cassidy, L.D.; Mayer, A.N.; Pritchard, K.A.; Oldham, K.T.; Gourlay, D.M. Intestinal alkaline phosphatase administration in newborns is protective of gut barrier function in a neonatal necrotizing enterocolitis rat model. J. Pediatric Surg. 2012, 47, 1135–1142.
- 122. Rentea, R.M.; Liedel, J.L.; Fredrich, K.; Pritchard, K.; Oldham, K.T.; Simpson, P.M.; Gourlay, D.M. Enteral intestinal alkaline phosphatase administration in newborns decreases iNOS expression in a neonatal necrotizing enterocolitis rat model. J. Pediatric Surg. 2013, 48, 124–128.
- 123. Rentea, R.M.; Liedel, J.L.; Fredrich, K.; Welak, S.R.; Pritchard, K.A.; Oldham, K.T.; Simpson, P.M.; Gourlay, D.M. Intestinal alkaline phosphatase administration in newborns decreases systemic inflammatory cytokine expression in a neonatal necrotizing enterocolitis rat model. J. Surg. Res. 2012, 177, 228–234.
- 124. Lee, C.; Chun, J.; Hwang, S.W.; Kang, S.J.; Im, J.P.; Kim, J.S. The effect of intestinal alkaline phosphatase on intestinal epithelial cells, macrophages and chronic colitis in mice. Life Sci. 2014, 100, 118–124.
- 125. Economopoulos, K.P.; Ward, N.L.; Phillips, C.D.; Teshager, A.; Patel, P.; Mohamed, M.M.; Hakimian, S.; Cox, S.B.; Ahmed, R.; Moaven, O.; et al. Prevention of antibiotic-associated metabolic syndrome in mice by intestinal alkaline phosphatase. Diabetes Obes. Metab. 2016, 18, 519–527.
- 126. Hamarneh, S.R.; Mohamed, M.M.R.; Economopoulos, K.P.; Morrison, S.A.; Phupitakphol, T.; Tantillo, T.J.; Gul, S.S.; Gharedaghi, M.H.; Tao, Q.; Kaliannan, K.; et al. A novel approach to maintain gut mucosal integrity using an oral enzyme supplement. Ann. Surg. 2014, 260, 706–715.
- 127. Alam, S.N.; Yammine, H.; Moaven, O.; Ahmed, R.; Moss, A.K.; Biswas, B.; Muhammad, N.; Biswas, R.; Raychowdhury, A.; Kaliannan, K.; et al. Intestinal alkaline phosphatase prevents antibiotic-induced susceptibility to enteric pathogens. Ann. Surg. 2014, 259, 715–722.
- 128. Van Veen, S.Q.; Dinant, S.; Van Vliet, A.K.; Van Gulik, T.M. Alkaline phosphatase reduces hepatic and pulmonary injury in liver ischaemia-reperfusion combined with partial resection. Br. J. Surg. 2006, 93, 448–456.

- 129. Malo, M.S.; Moaven, O.; Muhammad, N.; Biswas, B.; Alam, S.N.; Economopoulos, K.P.; Gul, S.S.; Hamarneh, S.R.; Malo, N.S.; Teshager, A.; et al. Intestinal alkaline phosphatase promotes gut bacterial growth by reducing the concentration of luminal nucleotide triphosphates. Am. J. Physiol.-Gastrointest. Liver Physiol. 2014, 306, G826–G838.
- Verweij, W.R.; Bentala, H.; Van Der Vlag, A.H.; Van Loenen-Weemaes, A.M.; Kooi, K.; Meijer, D.K.F.; Poelstra, K. Protection against an Escherichia coli-induced sepsis by alkaline phosphatase in mice. Shock 2004, 22, 174–179.
- 131. Van Veen, S.Q.; Van Vliet, A.K.; Wulferink, M.; Brands, R.; Boermeester, M.A.; Van Gulik, T.M. Bovine intestinal alkaline phosphatase attenuates the inflammatory response in secondary peritonitis in mice. Infect. Immun. 2005, 73, 4309–4314.
- 132. Kats, S.; Brands, R.; Hamad, M.A.S.; Seinen, W.; Scharnhorst, V.; Wulkan, R.W.; Schönberger, J.P.; van Oeveren, W. Prophylactic treatment with alkaline phosphatase in cardiac surgery induces endogenous alkaline phosphatase release. Int. J. Artif. Organs 2012, 35, 144–151.
- Khailova, L.; Robison, J.; Jaggers, J.; Ing, R.; Lawson, S.; Treece, A.; Soranno, D.; Osorio Lujan, S.; Davidson, J.A. Tissue alkaline phosphatase activity and expression in an experimental infant swine model of cardiopulmonary bypass with deep hypothermic circulatory arrest. J. Inflamm. 2020, 17, 27.

Retrieved from https://encyclopedia.pub/entry/history/show/55927