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Bioecology and pathogenicity of *Proteus* bacteria: A literature review

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Abstract. The role of *Proteus* bacteria in human and animal pathology has increased significantly in recent years, causing acute intestinal diseases, respiratory, hearing, nervous and urinary systems, as well as contributing to the formation of kidney and bladder stones, postoperative complications, and nosocomial infections. The persistence of some issues, such as their properties and interaction with the microbiocenosis, remains a subject of debate even after a long study of *Proteus* bacteria. The research aims to identify promising areas for further study of *Proteus* microorganisms. The information from scientific primary sources on the results of studying microorganisms of the genus *Proteus* was used for the analysis. The study results of *Proteus* bacteria performed by domestic and foreign scientists on the knowledge of their bioecology and potential pathogenicity factors (adhesins, toxins, haemolysins, etc.), characterisation of the positive role of proteins as biodegraders of harmful substances – bioremediators of proper environmental ecology; substantiation of promising areas for further research of bacteria of the genus *Proteus*, which will contribute to the development of an effective methodology for the prevention and treatment of diseases caused by them, the development of rational technologies for the use of their strains – bioremediators of the environment contaminated with harmful substances – are presented in the study. Further study of the genomic properties of *Proteus* bacteria will contribute to a clear understanding of the mechanisms of their potential pathogenicity factors and help to identify and understand the essence of the processes that contribute to the acquisition of new pathogenicity factors and drug resistance. The study of their interaction with representatives of the intestinal microbiocenosis of humans and animals will help to establish the nature of such interaction, determine the feasibility, prospects and rational directions in the creation of effective probiotics

Keywords: properties; swarming; pathogen; symbiont; biodegradation; promising areas of research

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Introduction

Bacteria of the genus *Proteus* are widespread prokaryotes in nature. They are often isolated from the intestines of clinically healthy humans and animals without any symptoms of disease, from various environmental objects such as soil, water, etc. (Al-Kubaisi & Al-Deri, 2022). The isolation of proteins from the intestines of clinically healthy mammals prompts some researchers to consider them representatives of the normal microflora of the macroorganism, but the arguments in this regard are insufficient. Currently, it would be more appropriate to consider such cases as bacterial carriers. However, it would be incorrect to categorically deny their possible belonging to the representatives of the intestinal microbiocenosis of macroorganisms in the future – the distinct plasticity of the biological properties of these prokaryotes, the presence of naturally circulating avirulent strains of them create prerequisites for the formation of the most rational variant of symbiosis with macroorganisms. At this stage of the phylogeny of proteins, the opinion of experts who consider them pathogens, causing a range of diseases in humans and animals, should be accepted. In particular, it concerns the naturally occurring *Proteus mirabilis*, which causes gastroenteritis and extraintestinal infections in humans, such as tympanitis, meningitis, urethritis, pyelonephritis, infectious cystitis, urolithiasis, etc. (Girlich *et al.,* 2020). In animals, proteins are also an etiological factor in gastrointestinal diseases, urinary tract, urolithiasis, etc. In humans and animals, they often cause postoperative complications, colonise medical instruments (mainly catheters) (Al-Sudani & Abdul-Kareem, 2023), and are also involved in foodborne toxicity (Gong *et al.,* 2019).

Potential pathogenicity factors of different proteus species have been studied in detail (Beltrão *et al.,* 2022; Liu *et al.,* 2023). Their nature and mechanism of pathogenic action have been characterised at an acceptable methodological level. This applies, in particular, to adhesins, toxins, haemolysins, and other factors (Girlich *et al.,* 2020; Gahlot *et al.,* 2022). At the same time, the circumstances (conditions) that affect the intensity of expression of genetic determinants of pathogenicity factors and the possible translocation of the latter within a species remain insufficiently characterised.

Effective prevention of infectious diseases, including those of protean aetiology, is possible only if the biology and ecology of their pathogens are fully comprehended. The basic biological properties of proteins have been thoroughly studied for a long time. Recently, molecular genetic mechanisms of protein film formation and drug resistance have been intensively studied (Akhter *et al.,* 2019). In this regard, it is promising to identify the facts and circumstances of the translocation of antibiotic resistance factors. Studies on the ecology of *Proteus* bacteria are also important. In this regard, their ecological niches have been identified and characterised both within populations of living beings and in various objects of the avital environment (Al-Kubaisi *et al.,* 2022). The results of the identification of protein strains capable of utilising harmful substances in a polluted environment are considered extremely encouraging. The creation of bioreanimator drugs based on them will allow us to address pressing environmental issues more effectively.

The data obtained by domestic and foreign researchers on the biology, ecology and pathogenicity factors of *Proteus* bacteria are not systematised, which hinders their effective use in the organisation of anti-epidemiological and anti-epizootic measures.

The research involved a comprehensive analysis of scientific sources aimed at studying the biological characteristics and pathogenic potential of *Proteus* bacteria. The search

and selection of literature included a thorough search in scientific databases such as Web of Science, Scopus, and PubMed and a selection of sources that best reflected the current state of research in this area. The sources were then systematised to create a coherent review. This included a thorough analysis and synthesis of information on the biology of Proteus bacteria, their role in natural and macrobiotic systems, and mechanisms of pathogenicity. The study will review both well-known and up-to-date articles to ensure that the research on this topic is complete and up to date. This approach allowed us to systematise and summarise the available knowledge and discoveries in this area, revealing key aspects of the bioecology and pathogenicity of bacteria of the genus *Proteus*. The research aims to analyse the literature reports on the bioecology and pathogenicity of bacteria of the genus Proteus and to identify promising areas for further research.

Systematics, morphology, culture, and enzymatic properties of *Proteus spp.*

According to the modern taxonomy of microorganisms, proteins are defined: Domain – *Bacteria*, Type – *Proteobacteria*, Class – *Gammaproteobacteria*, Order – *Enterobacteriales*, Family – *Enterobacteriaceae*, Genus – *Proteus*. Latter includes *P. vulgaris, P. mirabilis, P. penneri, and P. myxofaciens* (Brenner *et al.,* 2005).

Morphology. The *Proteus* bacteria are extremely polymorphic, as reported by the German microbiologist Hauser in 1885, who first identified and characterised the main morphological and cultural properties of *Proteus vulgaris* and *Proteus mirabilis* (Brenner *et al.,* 2005). Later, due to the improvement of microbiological research methodology, the emergence of more advanced equipment, in particular electron microscopes, the introduction of molecular genetic studies, etc., the ultrastructure and all other properties of proteins were studied in detail, revealing their biology, ecology and pathogenicity in great detail.

Proteus are gram-negative rods 0.4-0.6 μm by 1-3 μm in size, motile (peritrichs), do not form spores, and no typical capsules are detected. In the process of growth and proliferation, cells of different shapes, sizes and ultrastructure are also observed. The membrane of bacteria of the genus *Proteus* is virtually indistinguishable in its ultrastructural organisation from the cell membranes of other microorganisms of the family *Enterobacteriaceae*. Electron microscopy using cryotechnology reveals the outer and cytoplasmic membranes with a transparent periplasm 10.6-14.3 nm thick between them. The outer membrane is wavy, with a thin, 2-3 nm peptidoglycan layer intertwined. The cytoplasmic membrane is a thin bilayer structure closely adjacent to the periplasm. The proteins do not form typical capsules, but in *P. mirabilis* a capsular polysaccharide of fibrous structure with fibres located perpendicular to the cell surface was found. Lipopolysaccharide of the outer membrane (O-antigen) in *P. mirabilis* and *P. vulgaris*, in addition to monosaccharides typical for enterobacteria – glucose, glucosamine, D-glycero-D-manno-heptose, also contains galacturonic acid and, often, lysine (Brenner *et al.,* 2005). The peptidoglycan of *P. mirabilis*, unlike the peptidoglycan of other enterobacteria, is O-acetylated, which makes it resistant to lysozyme. The surface structures of bacteria of the genus *Proteus* are represented by flagella and fimbriae. Other structures (spines, curls) are also found (Gahlot *et al.,* 2022).

Culture and enzymatic properties. Proteins are facultative anaerobes, chemo-organotrophs, with both respiratory and fermentative metabolic types. They grow in the temperature range of 10-43°C. The temperature optimum for populations that exist as part of microbiocenoses in human or animal habitats is about

37°C. Proteins are undemanding to cultivation conditions, growing on simple nutrient media (pH 7.2-7.4). In meat and peptone broth, MPBs cause diffuse turbidity; in old cultures, sediment and a surface film are detected. On dense media, O-forms of the proteus form round, compact colonies, and H-forms are characterised by "creeping" growth, the medium is gradually covered with a kind of "veil" of smoky blue colour, which is called "swarming". During the latter process, the primary colony undergoes cell differentiation. Short rod-shaped bacteria (vegetative cells) differentiate into unsegregated multinucleated schwerm cells, ranging in length from 20-30 to 80-100 μm, with 50-500 times more flagella than their predecessors. The cytoplasm of the swarmer contains about 20 nucleoids. Compared to vegetative cells, swarmer cells are dominated by lipopolysaccharides (LPS) with long O-antigenic side chains, differences in the expression of some proteins and enzymes, and a markedly higher fluidity of the outer membrane (Allison *et al.,* 1994). The transformation of vegetative cells into swarmer cells is only the first phase of three observed during the swarming process. The next phases are "bacterial mass migration" and "consolidation" (Allison *et al.,* 1993). The migration of proteins on the surface of a dense medium is strictly multicellular. A group of swarmer cells rapidly migrates radially away from the colony on the surface of the dense medium. Gradually, their movement stops, and the swarmer cells differentiate into vegetative cells. The latter is called the consolidation phase. These phases are repeated, which is manifested by the formation of concentric rings on the surface of the medium. When swarmer cells are sown in a liquid medium, they differentiate into vegetative cells. The translocation of *P. mirabilis* cells on a dense surface is facilitated by a cell surface polysaccharide enriched with galacturonic acid and N-acetylgalactosamine, capsular polysaccharide (CPS), apparently due to a decrease in surface friction. The latter is substantiated by the fact that mutations in the 1112 bp gene encoding the enzymes necessary for the synthesis of LPS and the assembly of the above polysaccharide significantly inhibit cell migration (Gygi *et al.,* 1995). Based on the analysis of cell differentiation and group motility, a unique kinetic model of *P. mirabilis* swarming was developed, the key element of which is the proven dependence of the swarming process on cell age (Esipov & Shapiro, 1998). The differentiation of vegetative cells of uropathogenic *P. mirabilis* strains into schwerm cells is accompanied by an increase in the activity of some of their pathogenicity factors, in particular, extracellular haemolysin and metalloproteases, and intensification of invasion of urogenital epithelial cells (Allison *et al.,* 1993). Genetic analysis of the bases of *P. mirabilis* swarming shows that this process is regulated by at least 40-60 genes. Signalling molecules were found to initiate cell differentiation and migration. When studying the effect of 20 amino acids on the swarming process in proteins, it was proved that only glutamine can initiate this process on a minimal growth medium (Allison *et al.,* 1993). The authors consider glutamine to be a specific chemoattractant for swarming cells. Other factors, such as the viscosity of the medium and the presence of "anti-tagging" antibodies, are also likely to be involved in cell differentiation. It was found that with increased medium viscosity and the presence of antibodies, the rotational movement of flagella slows down, and abnormal differentiation of swarm cells is observed. It is believed that flagella function as tactile sensors of external growth conditions (Massad *et al.,* 1996).

Swarming is observed not only on solid media but also on the surface of many dense avital substrates, as well as in the macroorganisms contaminated with proteins – on

mucous membranes and other tissues (Brenner *et al.,* 2005). Proteins are characterised by a distinct enzymatic activity, in particular, they liquefy gelatin, peptidise milk, reduce nitrates to nitrites, decompose urea with the release of ammonia, etc. Based on the results of the enzymatic activity study, the genus of proteins within the Enterobacteriaceae family is determined and their species are identified.

Antigenic structure and pathogenicity factors of *Proteus spp*.

The antigenic structure of *Proteus* bacteria is complex, with O-, H- and, in some strains, K-antigens. The somatic (O-antigen) and flagellar (H-antigen) antigens of *P. mirabilis* and *P. vulgaris* have been characterised in detail. The chemical nature of the O-antigen is lipopolysaccharide. About 50 varieties of O- and about 20 H-antigens have been identified in proteins. Based on O-antigens, a methodology for determining the serogroup affiliation of clinical strains of proteins and serological diagnosis of diseases caused by them has been developed (Knirel *et al.,* 2011). However, this area requires further research because antigenically distinct strains are often isolated, especially among *P. penneri* (Palusiak, 2016).

The pathogenicity factors of bacteria of the genus *Proteus* are generally typical for members of the family *Enterobacteriaceae*. They ensure the ability of certain species (strains) to parasitise living organisms and cause pathological phenomena. Since the latter are most often observed under circumstances that lead to a weakening of the defence reactions of the human or animal body, proteins are classified as opportunistic microorganisms, and the diseases caused by them are called opportunistic infections. In the presence of pathogenicity factors, proteins adhere to the cell surface, colonising mucous membranes or the wound surface of the skin, form a biofilm, sometimes penetrate cells, and exert toxic effects directly on cells, tissues, organs and indirectly, causing a cascade of pathological phenomena in the infected macroorganism.

Regarding the representatives of the genus *Proteus*, it is worth noting their extremely pronounced biological plasticity, which contributes to the survival of bacteria in various environmental conditions and parasitism in humans and animals (Prystupa *et al.,* 2017). The latter is possible only if a particular strain has certain pathogenicity factors that provide it with virulence – the ability to penetrate the body and stay there, to resist the factors that maintain the latter's homeostasis, and to reproduce.

Adhesins. The primary phenomenon in the development of any infectious process caused by a pathogen is its adhesion to the surface of the epithelium or other cells in the macroorganism. It is ensured by physicochemical processes that occur when molecules located on the surface of the pathogen and molecules of the infected cells (tissues) come into contact. Only pathogens that synthesise adhesins, substances of protein or glycoprotein nature that are part of certain surface structures of their microbial cells, can attach to the cells of the latter reliably. In bacteria of the *Enterobacteriaceae* family, including Proteus, adhesins are concentrated mainly in the fimbriae (Massad *et al.,* 1996) and are characterised by a certain specificity – the ability to attach to the surface of certain cells (tissues) in an infected organism. An illustration of the latter can be found in strains of bacteria of the genus *Proteus*, which adhere intensively to urogenital epithelial cells. In this regard, it would be appropriate to assert that bacterial adhesins have a "targeted function", which is manifested by the pathogen's distinct tropism to certain tissues of the microorganism. Several types of fimbriae have been identified in representatives of the genus *Proteus*, which differ, in particular, in structure:

thick (7 nm in diameter) and thin (4 nm in diameter) (Armbruster *et al.,* 2012). The former is called MR/P *(Proteus-like fimbriae)*, and the latter are called MR/K (Klebsiella-like fimbriae). It was found that MR/P fimbriae provide more efficient adhesion of bacteria to epithelial cells compared to MR/K fimbriae (Silverblatt & Ofek, 1978). A 21 kDa protein isolated from MR/P fimbriae from *P. mirabilis* strain 3087 reacted intensively with urethral epithelial cells of the urinary tract *in vitro*. It was found that in the infected human body, it causes intensive colonisation of the kidneys and, as a result, pyelonephritis. MR/K fimbriae (MR/K haemagglutinins) differ from MR/P fimbriae not only in structure but also in their ability to bind to the tissues of the infected organism. They cause intensive adhesion of cells in the Bowman's capsule and basement membranes of the renal tubules and do not adhere to other epithelial cells of the urinary system. MR/K fimbriae are more common in *P. penneri* strains (Yakubu *et al.,* 1989).

In *P. mirabilis*, in addition to those described above, the following are also described: *"PMF fimbriae"*, "ambient temperature fimbriae" *(ATF)* and "uroepithelial cell adhesins". *PMF* fimbriae contain a polypeptide of 184 amino acids. It is believed that by recognising certain cell receptors in the infected organism, they ensure the adhesion of *P. mirabilis* to the bladder epithelium. A mutant of *P. mirabilis* that did not synthesise the above polypeptide colonised the bladder of experimentally infected mice to a much lesser extent compared to the field strain (Massad *et al.,* 1996). Ambient temperature fimbriae *(ATF)* are described by G. Massad *et al.* (1996). Electron microscopy revealed that they look like rod-like structures located on the surface of microbial cells. The main subunit of *ATF* fimbriae is a protein with a molecular weight of 24 kDa. The synthesis of ATF fimbriae depends on the culture conditions, in particular the temperature of the medium. Intensive expression of fimbriae in Luria broth occurred at a temperature of 23°C during the stationary phase of microbial culture growth. The pathogenetic significance of *ATF*-fimbriae has not been reported.

S.K. Wray *et al.* (1986) isolated a protein from the uropathogenic isolate *P. mirabilis HU 1069* and, having studied its properties, named it uroepithelial cell adhesin *(UCA)*. The researchers found that *UCA* adhesin is a polypeptide with a molecular weight of 17.5 kDa and causes bacterial adhesion to uroepithelial cells. I.G.W. Bijlsma *et al.* (1995), studying UCA adhesin synthesised by *P. mirabilis* strains isolated from dogs using electron microscopy, found that it has the appearance of thin fimbriae with a diameter of 4 nm. R. Pellegrino *et al.* (2013), using a wild type uropathogenic *P. mirabilis* strain that synthesised UCA adhesin and a *P. mirabilis* mutant that was unable to express UCA, confirmed in experiments on various biological models that UCA adhesin plays an important role in the colonisation of the urinary tract by *P. mirabilis*.

Proteins adhered to the cell surface can penetrate intracellularly under certain conditions. There is no convincing evidence that they possess the invasion factors characteristic of enterobacteria. However, the very fact of the ability of *Proteus* bacteria to penetrate macroorganism cells is well established. It has been proven that *P. mirabilis* and *P. vulgaris* invade *Vero* and *Hela* cells, mouse fibroblasts L-929 and human blood lymphocytes. The intensity of *P. mirabilis* invasion both *in vivo* and *in vitro* is stimulated by urea and correlates with the haemolytic activity of the strains. The ability of *P. mirabilis* to multiply in invaded cells of the permanent cell line L-929 and human blood lymphocytes has been experimentally confirmed (Peerbooms *et al.,* 1984).

Toxins. Bacteria of the genus *Proteus* synthesise endotoxins and exotoxins. The endotoxin is an outer membrane lipopolysaccharide

(LPS) (described previously as an O-antigen). Its pathogenic effect in an infected organism is similar to that of endotoxins of other gram-negative bacteria, characterised by pyrogenicity, the ability to cause hypotension, disseminated intravascular coagulation and lethal shock (Rózalski *et al.,* 2007). Its toxic effect on various cell types, including macrophages and lymphocytes, is realised through the lipid complex A, which is part of LPS. When it binds to the LPS-binding protein in the blood, it activates the CD14 receptor on macrophages, which leads to the intensive synthesis of biologically active mediators (TNF-α, IL-1, IL-6, IL-8 and IL-10). Depending on the level of expression of the latter, the effect in an infected organism can vary from beneficial adjuvant to toxic (Rietschel & Brade, 1992). Lipid A in *P. mirabilis* is considered to be an important factor of pathogenicity, characterised by mitogenic activity, lethal toxicity, and the ability to induce a local Schwartzman reaction (Sidorczyk *et al.,* 1983). A study has been published that proved the negative effect of LPS from *Proteus* bacteria on the activity of cytochrome P-450 enzymes in mouse liver (Kaca *et al.,* 1996). It is known that the destabilising effect on the latter, which is represented by a whole complex of enzymes and plays an important role in the metabolism of steroids, bile acids, unsaturated fatty acids, phenolic metabolites, as well as in the neutralisation of xenobiotics (poisons, drugs, etc.), leads to a disruption of physiological processes, which is manifested by a wide variety of pathophysiological phenomena in the infected organism.

Proteinases, urease, lecithinase. Other potential pathogenicity factors of proteins are their proteinases, hyaluronidase, urease, lecithinase, DNA and RNA nucleases. Protein strains isolated from patient materials are usually characterised by high proteolytic activity with a clear specificity for muscle and connective tissue proteins. They can hydrolyse gelatin, fibrin, albumin, and casein (Brenner *et al.,* 2005). The most pronounced biodestructive effect of these enzymes is observed when they are combined with microbial hyaluronidase. The latter, by destroying hyaluronic acid, causes increased tissue permeability in the infected organism, thus facilitating the migration of the pathogen.

The urease enzyme in *Proteus mirabilis* (PMU) consists of three subunits: PmUreα, PmUreβ and PmUreγ, formed into a quaternary structure. In the course of studying urease as a potential pathogenicity factor in bacteria of the genus *Proteus*, its significant role in the pathology of the kidneys and urinary organs was proved. In particular, it was found that *P. mirabilis* and *P. penneri* are involved in the formation of kidney and bladder stones due to the presence of urease (Rózalski *et al.,* 2007). As a result of urea hydrolysis caused by bacterial urease, the pH of urine increases, which leads to precipitation of its components – Mg^{2+} and Ca^{2+}. As a result, stones are formed, in particular struvite ($MgNH_4PO_4 \cdot 6H_2O$) (Broll *et al.,* 2021).

Immunoglobulin proteases. IgA protease has been found in *P. mirabilis, P. vulgaris* and *P. renneri* strains of different origin (Senior *et al.,* 1991). It has also been reported that a strain of *P. mirabilis* isolated from a patient with a chronic disease secreted a proteolytic enzyme that cleaved two classes of antibodies – IgA and IgG, as well as gelatin, casein, and bovine serum albumin. It turned out that proteases are metalloenzymes, the action of which is manifested in an alkaline environment, at a pH of 8 (Loomes *et al.,* 1992).

Lecithinase. The role of lecithinase as a pathogenicity factor in many bacteria is well known. *P. vulgaris* and *P. mirabilis* strains with pronounced lecithinase activity are often isolated from patients with signs of purulent inflammatory processes. Their O-forms produce the enzyme more intensively, especially during the period of dissociation of strains from the H-form to the O-form (Bozhko, 2012).

Haemolysins. Hemolysins are considered to be one of the leading factors in the pathogenicity of microorganisms. In bacteria of the genus *Proteus*, haemolytic activity correlates with the invasiveness of their strains (Peerbooms *et al.,* 1984; Rozalski *et al.,* 1993). Haemolysins of the *Proteus* genus belong to the family of pore-forming toxins (Braun & Focareta, 1991). There is enough information on the study of the haemolytic properties of bacteria of the genus *Proteus* to demonstrate the importance of this indicator, which has long been used as a marker of the pathogenicity of clinical strains. In a study of 84 strains of *P. mirabilis* and *P. vulgaris* isolated from patients with signs of urinary tract infection (UTI), it was found that the vast majority of them caused signs of *α-haemolysis* (greenish colouration around colonies) on dense medium (Kotełko *et al.,* 1983). The results of a study of the haemolytic properties of 126 strains of *P. mirabilis* and *P. vulgaris* isolated from various materials (from patients with signs of UTI, soil, etc.) are also reported. All studied strains haemolyse human and sheep erythrocytes during incubation in nutrient broth. The 10 strains of *P. mirabilis* studied under similar conditions also haemolyzed erythrocytes of guinea pigs, rabbits, mice, horses, cattle, and chicken (Kotełko *et al.,* 1983). A study of 45 strains of P. penneri revealed that they synthesised extracellular and/or cellular haemolysins (Senior *et al.,* 1991). The synthesis of extracellular haemolysin by *P. penneri* strains correlated with their cytotoxic activity determined *in vitro* on *Vero* cell lines and mouse fibroblasts L-929 (Rozalski *et al.,* 1993).

Siderophores are extremely important elements in the body of living things, including microorganisms. Prokaryotes, in the event of a deficiency of soluble iron in their environment, in particular in the human or animal body, synthesise and excrete their siderophores. The latter binds to iron and transports it into the microbial cell using transport mechanisms, thus causing iron deficiency in the infected microorganism, and weakening its resistance. In *P. mirabilis*, α-hydroxyisovaleric acid has been described as a siderophore (Rozalski *et al.,* 1993).

Peptidoglycan (murein) and a "capsular" acetylated highly hydrated polymer are also factors in the pathogenicity of the proteins. *P. mirabilis* peptidoglycan, unlike other enterobacteria, is glycosylated, which provides its resistance to lysozymes. It has been established that in the body of people infected with the protein, fragments of O-glycated peptidoglycan cause several pathological phenomena, including rheumatoid arthritis. The pathogenicity of *Proteus* bacteria also includes motility, film formation (Akhter *et al.,* 2019), and drug resistance.

Mobility. In the process of swarming, the proteins intensively colonise the epithelial membranes in the infected organism, forming biofilms that significantly protect them from immune defence factors and antibacterial drugs, in particular antibiotics. In addition, during this period, the activity of several other pathogenicity factors may increase. It was found that the differentiation of vegetative cells of uropathogenic *P. mirabilis* into schwerm cells is accompanied by an increase in the activity of extracellular haemolysin, urease, and metalloproteases (Allison *et al.,* 1994). It has also been reported that *P. mirabilis* swarmer cells, compared to vegetative cells, invade urogenital epithelial cells more intensively both *in vitro* and *in vivo* (Allison *et al.,* 1994). Recently, researchers devoted much attention to the study of virulence genes of pathogenic microorganisms, including the genus *Proteus*. It has been reported that the genetic profile of 36 clinical isolates of *Proteus mirabilis* isolated from patients with urinary tract infections in Brazil revealed the following genetic determinants of pathogenicity factors: mrpG, pmfA, ucaA, nrpG and pbtA (Beltrão *et al.,* 2022).

The pathogenicity factors described above are capable of providing certain strains with a parasitic mode of existence, usually in an insufficiently protected (immunologically weakened) human or animal organism. The design of pathogenicity factors in proteins is not stable within their species (strains). Some of them may be lost or, on the contrary, appear in the process of circulation of their strains in nature. The translocation of pathogenicity factors, as well as many other traits, occurs by mechanisms known in bacterial populations: transduction, conjugation, and transformation. Transmission of pathogenicity factors is possible both vertically – from parental individuals, and horizontally – to other strains and species. In the latter case, it is mainly due to plasmids. The above argues for the importance of continuous monitoring of the pathogenicity of clinical strains of proteins that cause diseases in humans and animals. Reliable information in this regard can be obtained both by using the modern methodology of molecular genetic testing of pathogenicity factors and the classical methodology based on the detection of phenotypic signs of virulence in clinical strains.

Protein-driven infection can be triggered by the pathogenic action of bacteria in the body's microbiocenosis or by exogenous infection. Autoinfection occurs mainly against the background of various other phenomena that weaken the immune system, including local (tissue) immunity, for example, in entero-, oral-, coronavirus, Escherichia coli or other infections, or under the influence of various toxic substances of avital nature, etc. Depending on the design of the strain in terms of the content of its virulence factors, the dose and site of penetration into the macroorganism, and finally, the immunoresistance of the latter and the nature of its exposure to environmental conditions, the pathogenesis and clinical manifestation of the disease may be different. This is clearly illustrated by the peculiarities of pathogenesis in urolithiasis and gastrointestinal disorders in humans and animals (Kroemer *et al.,* 2014; Vozianov *et al.,* 2016).

J.N. Schaffer *et al.* (2016) analysed the pathogenesis of urolithiasis and showed that *Proteus mirabilis* forms urease- and mannose-resistant clusters in the bladder of infected dogs and cats, which accumulate minerals, which is the starting point for the formation of urinary stones. The role of microbial urease in the formation of struvite stones in the kidneys and bladder of patients has already been reported. In addition to the above factors, glycocalyx substances (highly hydrated polymers on the surface of microbial cells) are also involved in the stone formation mechanism (Beynon *et al.,* 1992).

In the case of localisation of a protein-driven pathological process in the gastrointestinal tract, microbial toxins, in particular exotoxin, play a particularly important role in the pathogenesis of the disease. The thermolabile exotoxin synthesised by the protein penetrates intestinal epithelial cells via receptor-dependent endocytosis and causes several phenomena that activate adenylate cyclase, which begins to synthesise cyclic adenosine monophosphate (cAMP). The latter triggers a signalling pathway that leads to the outflow of chloride ions and other ions from the cell through CFTR channels and stops the entry of sodium ions into the cell. The latter are transported with water molecules, so their content in the cell is significantly reduced. Disruption of the water-salt balance leads to diarrhoea, intoxication, and related phenomena. In experiments using white mouse intestinal explants (Skibytsky, 1993), the toxic effect of *P. mirabilis* and *P. vulgaris* strains isolated from the intestine of a person with signs of gastrointestinal tract damage was manifested by the destruction of mucosal epithelial microvilli. A significant pathogenic role in the

gastrointestinal localisation of the process is also played by amino acid decarboxylation products: histamine, putrescine and cadaverine, which accumulate intensively as a result of the action of decarboxylases synthesised by proteins. Their pathogenic effect can also be intensified by the antagonism of proteins to representatives of the microbiocenosis of the contaminated biotope. In the case of mixed infection, in particular viral-bacterial infection, the pathogenesis of the disease can be much more complex, due to the nature of the direct interaction of proteins and other pathogens, or indirectly through the infected macroorganism.

Distribution of bacteria of the genus *Proteus* in the natural environment

To assess the epidemiological (epizootological) aspects of diseases caused by bacteria of the genus *Proteus*, in particular, to identify sources and factors of pathogen transmission, it is necessary to consider their ecological niches. First of all, the detection of *Proteus* in mammals. Bacteria of the genus *Proteus* are often isolated from the intestinal contents of humans and animals without any symptoms of disease. In particular, it has been reported that 4% of faecal samples from clinically healthy people contained bacteria of the genus *Proteus* (Bartges *et al.,* 1995). There have also been many reports on the isolation of *Proteus* from clinically healthy animals. Bacteria of the genus *Proteus* have been isolated, mainly from the intestinal contents, from gorillas (Bittar *et al.,* 2014), horses (Meyer *et al.,* 2010), cattle (Sadovsky, 1997), pigs (Kozlovska *et al.,* 2022), dogs (Liu *et al.,* 2023) and other animals.

Analysing the literature on the isolation of bacteria of the genus *Proteus* from various sources, D. Drzewiecka (2016) reports their isolation from various species of wild birds, including sparrows, blackbirds, white storks, wild turkey vultures, as well as from synanthropic rodents, snakes, bees, flies, cockroaches, aquatic animals – turtles and various fish species, including mackerel, freshwater Nile tilapia, tilapia from Lake Victoria, as well as from oysters and shrimps. *Proteus spp.* found in sea turtles near the Canary Islands in Spain have been identified as one of the causes of their deaths. *P. renneri* and *P. vulgaris*, isolated on Jekyll Island (USA), were found to be involved in embryonic mortality in turtles. The etiological role of *Proteus sp.* in the disease of alligators, which led to their death, was also proved. *P. hauseri* has also been reported to be involved in carp *(Cyprinus carpio)* disease (Kumar *et al.,* 2015).

Proteins are often found in food products (Al-Kubaisi *et al.,* 2022). In this regard, V.A. Bezugla (1975) carried out significant research in Ukraine. In the study of 1457 samples taken from slaughtered animals, she isolated 130 cultures of Proteus, which is 8.9% of the total number of samples examined. More than 70% of the isolates were identified as *P. mirabilis*, the rest were identified as *P. vulgaris*. Among the 365 *P. mirabilis* strains isolated, 105 (29.5%) were pathogenic to white mice, both by parenteral and enteral administration of the microbial culture. More than 60% of the isolated proteus cultures synthesised hyaluronidase, and more than 80% caused haemolysis of erythrocytes.

In a bacteriological study of 14 samples of minced meat and 38 samples of sausages (frankfurters) collected in the city's retail network, proteins were detected in seven cases (3.6%) – 2 strains of *Proteus vulgaris* from minced meat and 5 strains (4 strains of *Proteus vulgaris*, 1 strain of *Proteus mirabilis*) from the surface of sausages and frankfurters (Kozlovska *et al.,* 2022). It is also important to mention the positive role of *Proteus* species in the environment. Strains of *Proteus spp.* that protected legumes from the pathogenic *Fusarium moniliformae* and strains that produced volatile organic compounds that had a detrimental effect on nematodes, such as the soil-borne *Caenorhabditis*

elegans and the plant-pathogenic *Meloidogyne incognita*, have been identified (Lu *et al.,* 2014).

Many reports have been published on the important role of proteins in environmental bioremediation. In particular, the participation of *Proteus spp.* in the destruction of petroleum hydrocarbons in soil has been proven (Ibrahim *et al.,* 2013). The strains of *P. mirabilis* and *P. vulgaris* were found to be effective destructors of crude oil. A strain of *P. vulgaris* has been reported to be effective in utilising crude oil and diesel fuel (Olajide & Ogbeifun, 2010). A strain of *P. vulgaris* capable of reducing dichlorodiphenyltrichloroethane (DDT) to dichlorodiphenyldichloroethane (DDD) was isolated from the mouse intestine (Foght *et al.,* 2001). The ability of *Proteus sp.* to degrade dyes used in the textile industry has also been reported (Drzewiecka, 2016). Proteins are also related to the utilisation of heavy metals. In particular, a strain of *Proteus sp.* was found to be able to significantly reduce the concentration of the toxic metal Cr (VI) in seawater (Ge *et al.,* 2013).

Resistance to physical and chemical factors and drugs of bacteria of the genus *Proteus*

The global spread of proteins in nature is facilitated by their pronounced resistance to physical and chemical factors and drugs. Bacteria of the *Proteus* genus can adapt to survive in seawater. It has been reported that osmophilic (halotolerant) strains of *Proteus spp.* were isolated from the water of a Salt Lake in the Algerian Sahara (Hačene *et al.,* 2004). The resistance of bacteria of the genus Proteus to copper and other heavy metals has been reported (Ge *et al.,* 2013).

N. Rau *et al*. (2009) found *P. mirabilis* to be resistant to arsenic, copper, chromium, cobalt, cadmium, zinc, mercury, nickel, and lead. The sensitivity of proteins to drugs has been determined by many researchers. When antibiotic susceptibility of 100 strains of *Proteus mirabilis* isolated from urine was determined, 16 (16%) were found to be multidrug-resistant to cephalosporins. High resistance was observed concerning co-trimoxazole (97%), nalidixic acid (93%), cefotaxime (77%) and amoxicillin (62%). The highest susceptibility was observed for aminoglycosides, cephalosporins, glycopeptides, polypeptides, and macrolides in a study of antibiotic susceptibility of 20 strains isolated from animals in Ukraine (Aishpur *et al.,* 2016). They were less sensitive to penicillin. The genetic profile of 36 clinical isolates of *Proteus mirabilis* isolated from patients with urinary tract infections in Brazil revealed the presence of the following drug resistance determinants ($bla_{VIM,}$ bla_{IMP}, bla_{SPM}, $bla_{GES,}$ $bla_{OXA-23-like}$, $bla_{OXA-48-like}$, $bla_{OXA-58-like}$ and $bla_{OXA-10-like}$) (Beltrão *et al.,* 2022).

It has been proven that natural resistance to antibiotics is due to the ability of proteins to synthesise enzymes that inactivate antibiotics, in particular, β-lactamases: extracellular penicillinase, carbenicillin hydrolysing penicillinase, ampicillinase, etc. Resistance of naturally circulating strains is not a stable indicator and may change under certain conditions. Mechanisms of resistance modification may be associated with mutations in structural genes, recombination, and the acquisition or loss of R-plasmids (Luzzaro *et al.,* 2006).

An analysis of literature reports on the study of *Proteus* bacteria shows their widespread distribution in the environment and their involvement in diseases in humans, animals, and other living creatures, including amphibians and fish (Kumar *et al.,* 2015; Drzewiecka, 2016; Al-Kubaisi & Al-Deri, 2022). In humans, bacteria of the genus Proteus affect the digestive and respiratory organs, urinary tract, nervous system, etc. (Hamilton *et al.,* 2018). In animals, proteins are etiological factors of gastrointestinal diseases and the urinary tract, and often cause secondary infection in viral enteritis in newborn animals, etc. Proteins are also implicated

in foodborne toxicity (Gong *et al.,* 2019). Scientists have carried out many important studies concerning, in particular, the biology of bacteria of the genus *Proteus* (Esipov & Shapiro, 1998), factors of their pathogenicity (Armbruster *et al.,* 2012; Broll *et al.,* 2021; Gahlot *et al.,* 2022), in particular, film formation and drug resistance (Akhter *et al.,* 2019), pathogenesis of diseases caused by them in humans and animals (Schaffer *et al.,* 2016; Prystupa, 2017), and involvement in foodborne toxicity (Gong *et al.,* 2019).

Studies on the ecology of bacteria of the genus *Proteus* are also important. In this regard, their ecological niches have been identified and characterised both within populations of living beings (Drzewiecka, 2016) and in various objects of the avital environment (Lu *et al.,* 2014; Drzewiecka, 2016). The results of the identification of protein strains capable of utilising harmful substances in a polluted environment are extremely encouraging (Ibrahim *et al.,* 2013; Ge *et al.,* 2013). The development of bioremediation drugs based on them will allow us to solve urgent environmental problems more effectively.

The literature review shows that molecular genetic methods are widely used in the study of *Proteus* bacteria (Allison *et al.,* 1994; Beltrão *et al.,* 2022). The results obtained have allowed us to more clearly interpret important elements related to both the biology of proteins and the phenomena in nature caused by them, including diseases in humans and animals.

Conclusions

The study highlights the significant growth of the role of bacteria of the genus *Proteus* in the pathology of both humans and animals. They are known for their ability to cause a variety of diseases, including acute intestinal diseases, respiratory, hearing, nervous and urinary systems, and contribute to the formation of kidney and bladder stones. It is noted that bacteria of the genus *Proteus* have become active participants in nosocomial infections, which indicates their prevalence and potential threat to public health. The results of the literature review also reflect the positive role of Proteus bacteria in environmental bioremediation and the fight against harmful substances and emphasise the importance of further research in this area. It is determined that the study of their genomic properties and interaction with the intestinal microbiota of humans and animals is crucial for understanding the mechanisms of pathogenicity and the development of drug resistance. This will also contribute to the development of effective probiotics and rational technologies for the use of *Proteus* bacterial strains as bioremediators in the environment.

The presented analysis of literature reports shows the relevance of scientific research on bacteria of the genus *Proteus*. However, despite the long period of study of Proteus, a significant number of studies conducted at different methodological levels, several important phenomena related to both their biology and pathogenic potential remain insufficiently deciphered. The issues of understanding the mechanisms of possible antagonistic action of representatives of the ubiquitous gastrointestinal microflora against Proteus and the prospects for developing effective means of preventing excessive Proteus proliferation in human and animal habitats on their basis remain relevant. The methodology for diagnosing diseases of protean aetiology also needs to be improved. An important aspect of further research on proteins is to detail the conditions that affect the intensity of toxin formation in various products and animal feed.

The natural adaptive capacity of proteins argues for the importance of researching to further analyse the known and likely ecological niches for them. The latter concerns, first of all, various water bodies, in particular, the determination of conditions that affect the intensity of inter-population and interspecies

translocation of genetic determinants of pathogenicity and drug resistance. Intensification of research on interspecies communication, detailing the factors and circumstances that regulate its nature and consequences would certainly contribute to the identification of rational directions in the development of an optimal methodology for controlling the pathogenicity of naturally occurring bacteria of the genus *Proteus*, minimising the growth of their resistance to antimicrobial agents. Further study of proteins as potential utilisers of harmful substances in terms of developing effective environmental bioremediators remains extremely important.

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Conflict of Interest

None.

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Біоекологія та патогенність бактерій роду *Proteus*: літературний огляд

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Анотація. В останні роки значно зросла роль бактерій роду *Proteus* у патології людини і тварин, спричинюючи гострі кишкові захворювання, ураження органів дихання, слуху, нервової та сечовивідної систем, а також сприяючи утворенню каменів у нирках і сечовому міхурі, післяопераційним ускладненням та нозокоміальним інфекціям. Втриманість деяких питань, таких як їхні властивості, взаємодія з мікробіоценозом, залишається предметом дискусій навіть при тривалому вивченні бактерій роду *Proteus*. Мета роботи – визначення перспективних напрямів подальшого вивчення мікроорганізмів роду *Proteus*. Було використано для аналізу інформацію в наукових першоджерелах про результати вивчення мікроорганізмів роду *Proteus*. У статті викладені результати досліджень бактерій роду *Proteus*, виконаних вітчизняними та зарубіжними науковцями, щодо пізнання їх біоекології та потенційних факторів патогенності (адгезинів, токсинів, гемолізинів та ін.), охарактеризовано позитивну роль протеїв як біодеградантів шкідливих речовин – біореаніматорів належної екології довкілля; обґрунтовано перспективні напрями подальшого дослідження бактерій роду *Proteus*, які сприятимуть розробці ефективної методології профілактики та лікування обумовлюваних ними захворювань, розробці раціональних технологій використання їх штамів – біореаніматорів забрудненого шкідливими речовинами довкілля. Подальше вивчення геномних властивостей бактерій роду *Proteus* сприятиме чіткому розумінню механізмів реалізації потенційних їх факторів патогенності, допоможе виявляти та розуміти суть процесів, що сприяють набуттю ними нових факторів патогенності, резистентності до лікарських засобів. Вивчення взаємодії їх із представниками кишкового мікробіоценозу людини і тварин дозволить встановити характер такого взаємовпливу, визначить доцільність, перспективи та раціональні напрями у створенні ефективних пробіотиків

Ключові слова: властивості; роїння; патоген; симбіонт; біодеградація; перспективні напрями досліджень