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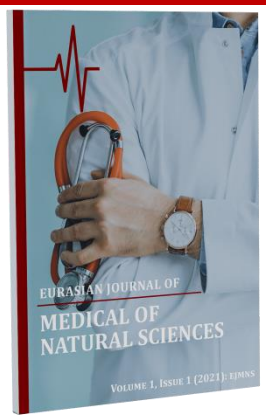

REVIEWING THE CURRENT LANDSCAPE OF PROBIOTICS IN TREATING INFECTIOUS DISEASES

Khusanova Mukaddas Aktamovna
Senior assistant at the Medical faculty of the "Alfraganus" University
Email: xusanova.m7308@mail.ru
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ABSTRACT

This review provides an overview of the potential of probiotics as a clinical intervention for infectious diseases by examining research and development efforts over the past two decades, as reflected in patents and clinical trials. Data were collected from patent and clinical trial databases to assess the long- and short-term trends in probiotics research. Analysis included the total number of patents and trials for each indication, application dates and locations, and types of applicants/sponsors. A total of 22 infectious diseases were investigated, resulting in 82 patents and 65 clinical trials targeting 18 indications. A consistent increase was observed in the number of patents and clinical trials since 1999, with the highest number focusing on digestive tract, respiratory, and urogenital indications. The findings indicate significant interest in probiotics for infectious diseases, aligning with reported unmet needs and global probiotics sales estimates. However, a decreasing rate of translation from patents to clinical trials suggests potential barriers in the research process.

Introduction

As recently as 2019, infectious diseases like lower respiratory tract infections, diarrheal diseases, and tuberculosis persisted among the top 10 global causes of death and disability-adjusted life years (DALYs) (Global Health Observatory, 2021). Noteworthy outbreaks such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and the ongoing COVID-19 pandemic underscored the increasing prevalence of zoonotic diseases (Skowron et al., 2022). Moreover, the incidence and impact of lower respiratory tract infections are expected to escalate within our aging population, posing significant challenges to healthcare systems if unaddressed (Feddema et al., 2021). In 2018, the economic toll of infectious disease epidemics was estimated at approximately US$60 billion annually, with the

ongoing COVID-19 pandemic costs projected to soar to US$16 trillion (Cutler and Summers, 2020; Wellcome, 2021).

Even as years have passed since the pandemic's onset, its repercussions endure. Despite challenges such as a dearth of understanding about the emerging virus (Janse et al., 2021), numerous vaccines have been developed, exhibiting short-term efficacy and effectiveness (Noor, 2021; Whitaker et al., 2022). Yet, uncertainties persist regarding long-term efficacy, and curative medications, while in development, remain unavailable (Couzin-Frankel, 2021; Kane and Kounang, 2022). Additionally, the World Health Organization (WHO) reports disruptions in immunization programs due to the pandemic, potentially leading to increased vaccine-preventable diseases among young children (World Health Organization, 2020). Furthermore, antimicrobial resistance is escalating, diminishing the effectiveness of antibiotic interventions developed to combat infectious diseases (Peri et al., 2019). Hence, there is a pressing need for novel interventional and prophylactic approaches to alleviate the burden of infectious diseases.

Maintaining and potentially restoring the microbiota of humans is regarded as crucial for the resilience of both humans and animals, offering protection against various infectious and inflammatory diseases (Larsen and van de Burgwal, 2021). Probiotics, defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" (World Health Organization, 1999, p. 8), have shown promise as a clinical intervention for numerous infectious diseases, potentially including COVID-19 (Lei et al., 2017; Infusino et al., 2020). Research indicates that probiotics may be beneficial for infectious diseases due to their positive effects on the host's microbiota, which can lead to various other health benefits (Valdez et al., 2014; Reid, 2017; Liu et al., 2018; Infusino et al., 2020). The primary target for probiotics thus far has been the gut microbiota, given its significant contribution to immune system development and its status as the largest immune organ in the human body (Ubeda and Pamer, 2012). However, promising outcomes have also been observed for other microbiota, such as the lung microbiota, where probiotics exert their effects through the gut-lung axis (Dumas et al., 2018; de Oliveira et al., 2021).

Probiotics can alter the human gut microbiota in several ways, including enhancing antiviral activity following vaccination (Yeh et al., 2018; Infusino et al., 2020), and preventing and/or treating respiratory tract and urogenital infections by inhibiting bacterial adhesion and enhancing mucosal barrier function (Reid, 2017; Liu et al., 2018; Stavropoulou and Bezirtzoglou, 2020; Lv et al., 2021; Theodosiou et al., 2021). The significance of the gut microbiota is further underscored in the context of COVID-19, as the virus affects not only the respiratory tract but has also been associated with reduced gut microbiota diversity due to interactions between the respiratory and digestive tracts, known as the gut-lung axis (de Oliveira et al., 2021). Although research on the relationship between COVID-19 and the gut microbiota is still emerging, probiotics have been suggested to potentially enhance the recovery of hospitalized COVID-19 patients compared to those not using probiotics (Zhang L. et al., 2021). However, numerous clinical trials are ongoing, complicating the comprehensive assessment of probiotics' benefits for COVID-19 (Kurian et al., 2021).

In summary, probiotics hold promise as an intervention for infectious diseases. Alongside their potential clinical effectiveness, research has demonstrated the safety of orally

consumed probiotics (van den Nieuwboer et al., 2014, 2015a,b; Larsen et al., 2017). As a result, probiotics could become interventions with a favorable benefit-to-burden ratio. However, concerns persist regarding efficacy due to conflicting findings across clinical studies (Suez et al., 2019). These discrepancies may stem from various research barriers, including differences in strain potency and user characteristics such as dosage (Suez et al., 2019). Additionally, probiotic species can exert their effects through diverse mechanisms, such as fermentation and antibiotic production, further complicating efficacy assessments (Suissa et al., 2022). Moreover, carrier matrices can impact probiotic efficacy (Flach et al., 2018). Consequently, making generalized statements about probiotic efficacy is challenging due to these factors (Flach et al., 2018; Lebeer et al., 2018). Nonetheless, the field of probiotics is rapidly advancing. Overall, the current understanding of probiotics' effectiveness remains uncertain, leaving unanswered questions about their most beneficial applications, not only for COVID-19 but also for other infectious diseases.

An effective approach to grasp the current state of the field is to examine intellectual property and ongoing clinical trials. Patents serve as early indicators of market developments and emerging technologies, offering insights into long-term research trends as they provide intellectual property protection for 20 years (Feddema and Claassen, 2018; Janse et al., 2020). On the other hand, clinical trials offer a snapshot of late-stage research progress, serving as essential steps preceding market entry and providing short-term insights into ongoing research efforts (Janse et al., 2020). In line with this perspective, this review aims to comprehensively assess the state of probiotics and infectious diseases by analyzing relevant patents and clinical trials conducted over the past two decades.

Materials and Methods

To explore the utilization of probiotics for the prevention, treatment, or mitigation of symptoms associated with infectious diseases, we examined both patent and clinical trial databases. Patents serve to safeguard the intellectual property of novel inventions, making them a reflection of early-stage applied research endeavors (Janse et al., 2020). On the other hand, clinical trials represent the culmination of late-stage research efforts, being conducted towards the conclusion of the research and development process prior to market introduction (Ramezanpour et al., 2015; Janse et al., 2020). Collectively, these databases offer insights into the progression of the research field.

Selection and Categorization of Infectious Diseases

We conducted searches in patent and clinical trial databases to identify entries combining probiotics with infectious diseases. To define infectious diseases comprehensively and ensure the inclusion of a diverse range of conditions, we consulted relevant literature sources to compile an extensive list (Shetty et al., 2009; Webber, 2019; University of Utah Health, 2021). A comprehensive table was developed in collaboration with a medical microbiology expert to establish a thorough foundation for this investigation. A total of 80 infectious diseases and infections, along with their microbiological classifications, were categorized into nine distinct groups based on their most prevalent clinical symptoms (Supplementary Table 1).

According to Nelson (2014), clinical classification relies on identifying a disease's predominant clinical manifestation, which can be pivotal in selecting appropriate treatments.

Given that our research focused on treatment, prevention, immune response enhancement, and symptom alleviation, this classification methodology was deemed most beneficial compared to other conventional approaches such as microbiological or transmission-based classification. However, due to the varied nature of certain infectious diseases, multiple classification options were available, such as infectious diarrhea, Escherichia coli, and Clostridium difficile infections. In such cases, we adopted the most commonly cited classification found in the literature. Additionally, certain diseases like infectious diarrhea and nosocomial infections may have multiple potential causative agents. To encompass these possibilities, no further specifications were applied, and the most prevalent causative pathogens (e.g., norovirus, rotavirus, E. coli, and Salmonella spp.) were listed separately. The classification of systemic symptoms was based on the definition provided by the United States National Library of Medicine (NLM) Medical Encyclopedia, referring to infectious diseases that "affect the entire body, rather than a single organ or body part" (NLM, 2021, para. 1).

Collection of Patent and Clinical Trial Data

To identify pertinent patents, this study utilized the European Patent Office (EPO) Espacenet database, renowned for its extensive coverage of patents, encompassing over 130 million patents from various countries and organizations globally (Jürgens and Herrero-Solana, 2015). For the identification of relevant clinical studies, searches were conducted on the EU clinical trials register (CTR.eu), the United States NLM database (CT.gov), and the International Clinical Trials Registry Platform (ICTRP). These databases were chosen due to their regular updates and comprehensive coverage, collectively spanning 202 countries and encompassing 17 distinct clinical trial databases (World Health Organization, 2021). This selection aligns with previous studies in the field (Ramezanpour et al., 2015; Janse et al., 2020; Neevel et al., 2020).

To ensure thorough coverage of relevant patents, expert guidance was sought from the Dutch Patent Office, a division of the Netherlands Enterprise Agency (RVO). International Patent Classification (IPC) codes and Cooperative Patent Classification (CPC) codes were both employed to select pertinent patent codes (Table 1). Search queries were crafted for each infectious disease, incorporating the patent classification codes outlined in Table 1 (Espacenet, 2019), followed by the disease's name and, where applicable, its common name or abbreviation.

Table 1

Overview of included patent classification codes.

CPC/IPC code	Description Espacenet
A61K2035/115	“Probiotics”
A61K35/741	“Probiotics (probiotic yeast, e.g., saccharomyces)”
A61K35/742	“Spore-forming bacteria, e.g., *Bacillus coagulans*, *Bacillus subtilis*, clostridium or *Lactobacillus sporogenes*”
A61K35/744	“Lactic acid bacteria, e.g., enterococci, pediococci, lactococci, streptococci or leuconostocs”
A61K35/745	“Bifidobacteria”
A61K35/747	“Lactobacilli, e.g., *L. acidophilus* or *L. brevis*”

A23L33/135	“Bacteria or derivatives thereof, e.g., probiotics”

For clinical trial data collection, a similar methodology was employed, with specific queries devised for each infectious disease. To ensure the trials focused on probiotic interventions, search queries in clinical trial databases incorporated a list of the most commonly utilized probiotic microorganisms, including terms such as “Probiotic,” “Probiotics,” “lactobacillus,” “streptococcus,” “bifidobacterium,” “enterococcus,” “Escherichia,” “e coli,” “saccharomyces,” and “lactic acid bacterium.” Extensive testing of search queries was conducted to optimize their effectiveness. It was observed that wildcard operators (*) had little impact on the relevance of results or sometimes led to inaccuracies, thus they were omitted from the queries. The final database searches were conducted on November 15, 2021.

Patent and Clinical Trial Data Selection

Selection of patent and clinical trial data involved a manual screening process of titles to determine suitability. Subsequently, for patents, a secondary screening of abstracts, descriptions, and claims was conducted within the Espacenet database to ensure adherence to inclusion criteria. The following criteria were applied for both patents and clinical trials:

- Publication between January 1, 1999, and November 15, 2021.
- Description of live probiotics intended for oral ingestion (excluding killed microorganisms or derivatives thereof).
- Relevance to the enhancement of post-vaccination immune response, treatment, prevention, or alleviation of symptoms of infectious diseases.
- For patents: exclusion of those solely detailing production methods or technologies.
- For clinical trials: adherence to an interventional study design.

The chosen timeframe of 1999 to 2021 allowed for a comprehensive overview of the past two decades. Due to the 18-month delay between patent filing and publication, as well as disruptions caused by the COVID-19 pandemic, data beyond May 2020 were not considered for definitive conclusions. Additionally, patents or clinical trials involving killed microorganisms or their derivatives were excluded, as they did not align with the WHO definition of probiotics.

Patent and Clinical Trial Analysis

Analysis of patent and clinical trial data was primarily conducted using Microsoft Excel. Full patent documents available in the Espacenet database were consulted for detailed patent analysis. The key aspects examined in the patent and clinical trial analysis included the following: the total number of included results, the nature of the applicant or sponsor (industrial, academic, individual, government, or collaborative), year of publication, and geographical distribution.

Each individual patent and clinical trial entry was carefully reviewed to determine the number of results associated with each infectious disease. These entries were then coded with the names of all mentioned indications. To enhance visualization clarity, indications were categorized based on their clinical manifestations. Similarly, applicant and sponsor types were coded by analyzing each included patent and clinical trial, utilizing extracted data or full patent documents when necessary.

Application or start years were readily available, and countries of patent application or clinical trial execution were identified using the country (or organization) codes associated

with each patent. This information was gathered from all patent numbers listed under "also published as" and the indicated locations of clinical trials, respectively.

Results

Patent and Clinical Trial Inclusion

Out of 782 patent documents retrieved from Espacenet for all relevant infectious diseases, 125 were deemed suitable for analysis. The primary reasons for exclusion included patents describing production processes, focusing on other disease types such as chronic and autoimmune conditions, utilizing probiotic derivatives instead of live organisms, or lacking any mention of probiotics. The analysis of included patents involved examining the indicated infectious disease(s), the country of patent application, the type of applicant, and the application date.

Regarding clinical trials, out of 658 trials identified for the relevant infectious diseases, 124 met the inclusion criteria for analysis from CT.gov, CTR.eu, and the ICTRP. Clinical trials were excluded if the indication stated in the title was not related to an infectious disease or if the specified intervention did not involve probiotics. The analysis of included clinical trials encompassed the number of trials focusing on each infectious disease, their respective locations, the type of sponsor, and the starting year.

Patent and Clinical Trial Trends

The majority of patents were associated with infectious diseases manifesting in digestive tract symptoms (46.5%) and urogenital symptoms (19.2%), which included notable pathogens such as E. coli (n = 86), Helicobacter pylori (n = 80), bacterial vaginosis (n = 73), and C. difficile (n = 70), as depicted in Figure 1. The top five infectious diseases with the highest number of patent results were all related to digestive tract and urogenital infections, whereas the top 10 also encompassed upper respiratory tract infections (influenza, n = 74) and oral infections (periodontitis, n = 49). In contrast, fewer relevant patents were identified for most parasitic infections, zoonoses, tropical diseases, and newly emerging infectious diseases (totaling n = 35). Among the included clinical trials, the majority were centered around infectious diseases characterized by digestive tract symptoms (43.4%), urogenital symptoms (20.7%), and respiratory symptoms (18.8%), with the highest number of trials focusing on H. pylori infection (n = 74), antibiotic-associated diarrhea (n = 62), and bacterial vaginosis (n = 56; Figure 1). This was followed by pneumonia (n = 43) and urinary tract infections (n = 41). Additionally, there were 33 clinical trials and 28 patents specifically targeting probiotic applications for COVID-19.

Regarding the initial year of application for each patent and clinical trial, there was an upward trajectory in the total numbers of patents and clinical trials since 1999 (Figure 2A). Examining the ratio of clinical trials to patents (CT/P) per year revealed an ascending trend from 2000 to approximately 2017, followed by a slight decline from around 2014 to roughly 2018 (Figure 2A). Categorizing patents based on the clinical manifestation of infectious diseases, applications of probiotics targeting digestive tract symptoms have remained the most prevalent since 1999, followed by those addressing urogenital symptoms (Figure 2B). Similarly, clinical trials exhibited a comparable pattern to patents concerning infectious diseases with respiratory tract and urogenital symptoms; however, there was a greater emphasis on clinical trials involving probiotics for infectious diseases with respiratory

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symptoms and a lesser focus on those affecting the skin (Figure 2C). Notably, both patents and clinical trials relating to probiotic applications for infectious diseases involving the central nervous system, ear, nose and throat, systemic issues, skin ailments, cardiovascular conditions, and hemorrhagic fevers demonstrated slower cumulative growth (Figures 2 B, C).

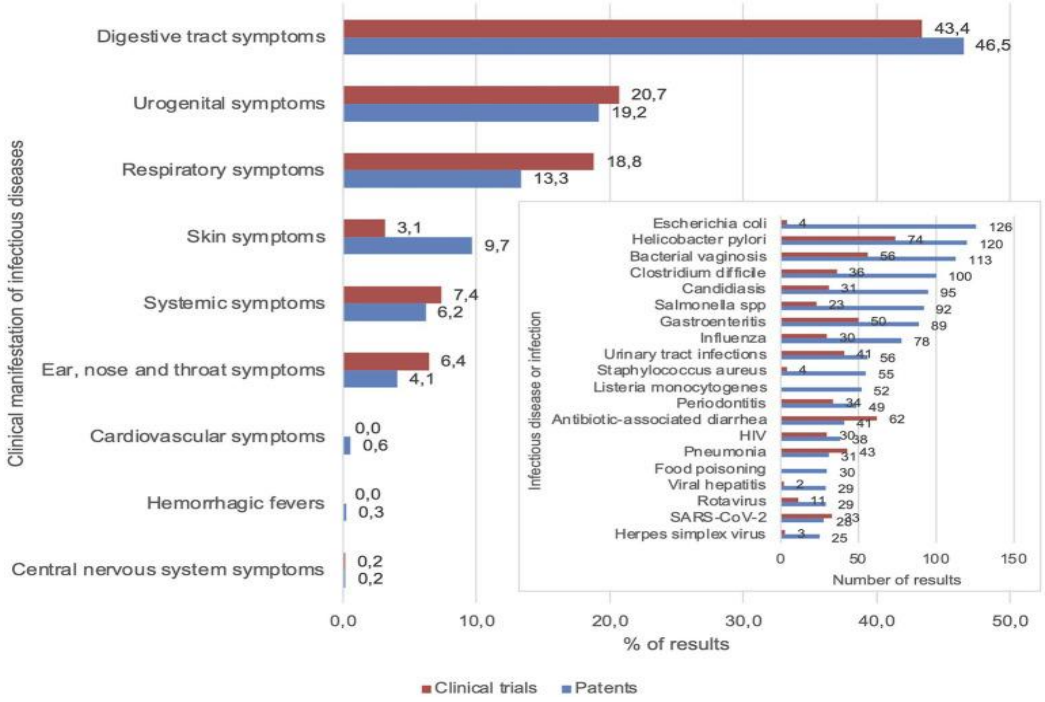

Figure 1

Focal points of patents and clinical trials were digestive tract, urogenital, and respiratory symptoms. Percentages of patent and clinical trial results for each category of infectious diseases based on clinical manifestation. The 20 infectious diseases that were mentioned most frequently in patents are displayed in the insert graph .

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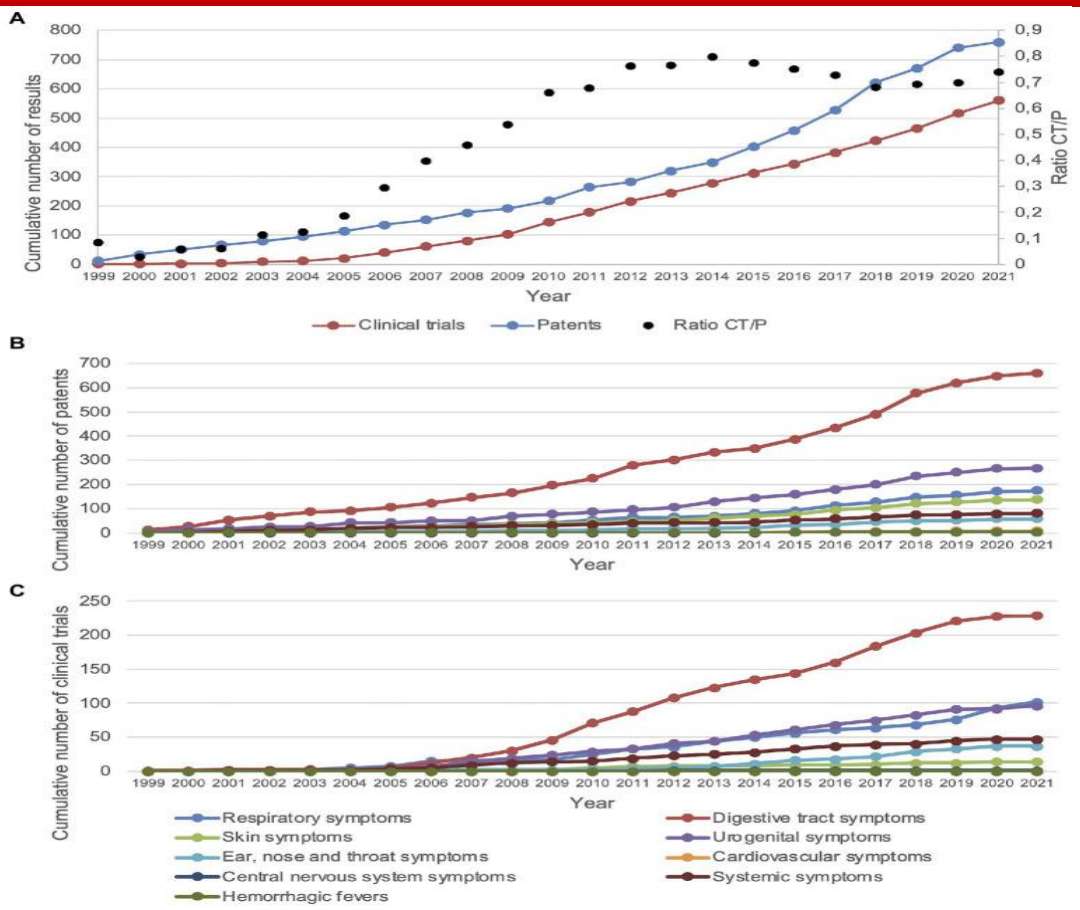

Figure 2 Patents and clinical trials showed an increasing trend since the year 2000. **(A)** CT/P = clinical trials/patents. Displayed are the cumulative number of patents and clinical trials as well as the ratio of clinical trials and patents. **(B)** Cumulative number of patents for each group of clinical symptoms of infectious diseases. **(C)** Cumulative number of clinical trials for each group of clinical symptoms of infectious diseases. Cardiovascular and central nervous system symptoms are obscured due to overlap with hemorrhagic fevers. The years 2020 and 2021 may not be complete due to the 18-month patent application period and COVID-19-related disruptions.

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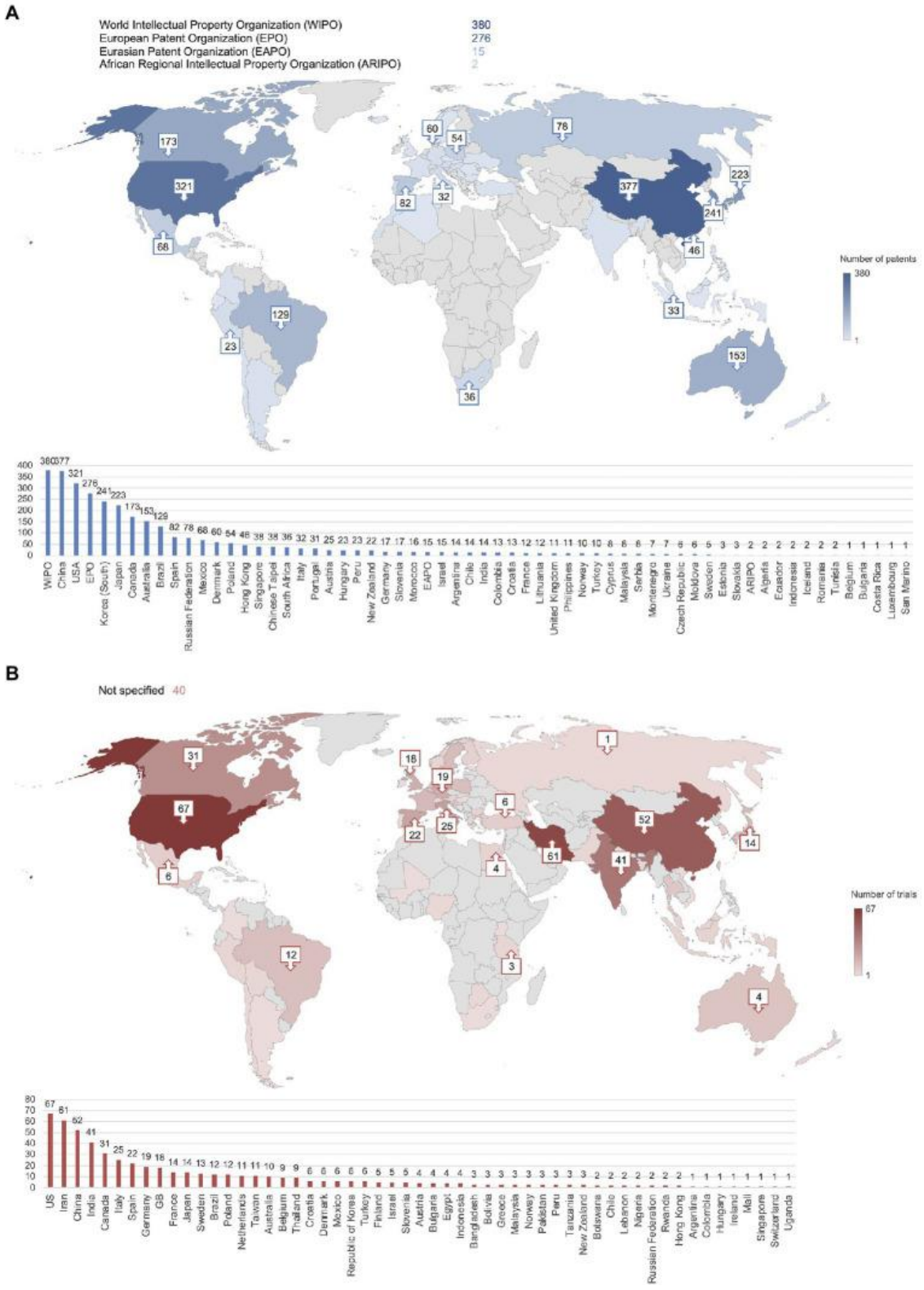

Figure 4

China, the United States, South Korea, and Iran were the most frequently reported locations of patent applications and clinical trials. **(A)** Number of patent applications per country or organization. Total exceeds $n = 789$ due to most patents being applied for in multiple countries. **(B)** Number of clinical trials per country. Numbers not shown on the map are included in the bar graph.

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Patent and Clinical Trial Applications

Examining the countries of application for each patent, the primary locations were in Asia and North America, with the highest number of patents filed in China (n = 377), followed by the United States of America (n = 321) and Korea (n = 241; Figure 3A). Additionally, 380 patents were applied for at the World Intellectual Property Organization (WIPO), 276 at the European Patent Office (EPO), 15 at the Eurasian Patent Organization (EAPO), and 2 at the African Regional Intellectual Property Organization (ARIPO). Figure 4B illustrates that the principal locations for clinical trials were also in Asia and North America, with the United States of America leading (n = 67), followed by Iran (n = 61), China (n = 52), India (n = 41), and Canada (n = 31). Overall, clinical trials appeared to be more geographically distributed than patent applications; however, 40 clinical trial records did not specify a location.

In addition to examining the patent application country and trial location, the types of applicants and sponsors were scrutinized (Figure 4). More than half of the patents were attributed to industrial applicants (n = 437, 56.1%), representing the largest cohort, succeeded by academic applicants (n = 133, 17.1%), individual applicants (n = 81, 10.4%), and collaborations between industry and individuals (n = 48, 6.2%) or academia (n = 44, 5.6%). Governmental organizations accounted for the fewest number of patents (n = 34, 4.4%). Regarding the sponsors/collaborators of the clinical trials, over half were funded by academic entities (n = 313, 52.0%). The second-largest sponsor group comprised industrial entities (n = 96, 15.9%), followed by collaborations between academia and industry (n = 84, 14.0%) and governmental entities (n = 81, 13.5%). The smallest number of clinical trials was sponsored by individuals (n = 11, 1.8%) and collaborations between industry and individuals (n = 7, 1.2%). Some trial records did not specify a sponsor or collaborator (n = 10, 1.7%).

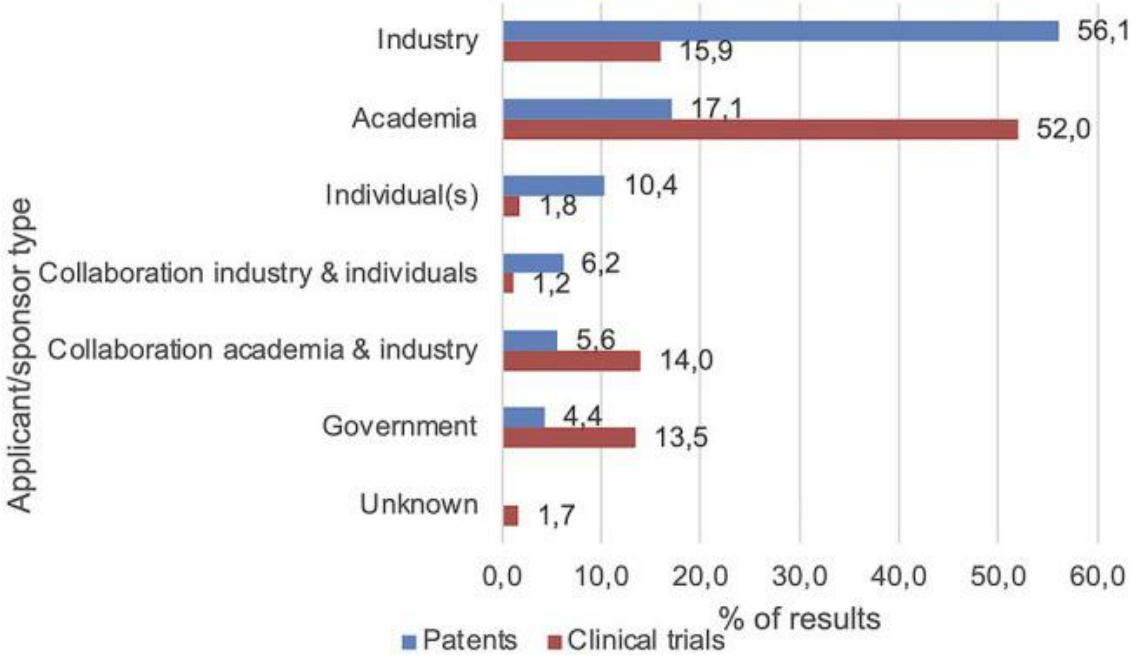

Figure 4

Main applicant/sponsor types included industry and academia. Values represent percentages of the number of included patents and clinical trials, respectively.

Discussion

This study provides an analysis of the current landscape concerning patents and clinical trials related to probiotics for infectious diseases. Our research encompassed 789 patents and 602 clinical trials primarily focusing on infectious diseases with symptoms affecting the digestive tract, urogenital system, and respiratory system. The significant growth in both patents and clinical trials from 1999 to 2021 indicates a substantial interest in probiotics as potential clinical interventions for infectious diseases, particularly in Asia and North America, drawing attention from both industrial and academic sectors.

Over the past two decades, we observed a slight disparity between the cumulative increase in patents describing probiotic applications for infectious diseases and the growth in the number of clinical trials. While the cumulative number of patents appears to have reached a plateau, clinical trials have continued to rise steadily, with no apparent sign of saturation until 2021. Drawing from Fernald et al.'s (2013) concept of the technology saturation curve (S-curve) initially proposed by Ernst (1997), which illustrates technological evolution within an industry across four stages: Emerging, Growth, Maturity, and Saturation (Weenen et al., 2013), our data suggests that the probiotics industry, as reflected by the cumulative number of patents, has likely entered the maturity stage. However, this assessment remains provisional and awaits confirmation from future data, as external factors such as the COVID-19 pandemic and the 18-month patent application process could introduce delays and potential alterations to this trajectory.

In terms of clinical trials, the cumulative count over the past two decades exhibited a less pronounced growth trajectory, showing no indication of reaching a plateau. This suggests that, according to the S-curve framework, the maturity stage has yet to be attained. The lag observed between patents and clinical trials may stem from various factors. Firstly, as noted by van de Burgwal et al. (2018), the process of patent application typically precedes the execution of clinical trials in the research continuum. Additionally, the patent application process is comparatively less arduous and costly than conducting clinical trials, potentially leading to the abandonment of new probiotic products during early-stage development due to stringent regulatory requirements in probiotics research (van den Nieuwboer et al., 2016; Binda et al., 2020). Consequently, this could create a disparity between the number of patents filed and the number of clinical trials initiated.

Infectious diseases characterized by digestive tract symptoms exhibited the most substantial growth in both patents and clinical trials, making them the predominant indications overall. This emphasis on digestive tract symptoms aligns with the direct interaction between probiotics and the gut microbiota of the host, as well as pathogens (Cazorla et al., 2018; Lv et al., 2021; Taverniti et al., 2021). Furthermore, these findings corroborate a previous study by van den Nieuwboer et al. (2016), which highlighted the high priority of conditions related to the digestive tract, such as antibiotic-associated diarrhea, among key opinion leaders (KOLs) in the probiotics field.

The second and third highest numbers of patents and clinical trials were observed for infectious diseases with urogenital and respiratory symptoms, respectively. The susceptibility to these diseases has been linked to the microbiome composition in both young children and older adults (Horwitz et al., 2015; Unger and Bogaert, 2017). According to the study on unmet

needs and research priorities by van den Nieuwboer et al. (2016), respiratory infections in infants and children held a medium research priority, while it was low for adults, aligning with the observed percentages of patents and clinical trials. The exception to this trend is the significant number of clinical trials investigating the effects of probiotics on COVID-19 (n = 33) in the past two years, reflecting the emergence of the COVID-19 pandemic after the publication of van den Nieuwboer et al.'s research. As for the research priority of infectious diseases with urogenital symptoms, comparisons with the findings of van den Nieuwboer et al. (2016) are challenging due to the lack of specific articulation, likely stemming from either low prioritization or the use of alternative terminology.

Investigation into termination and specification revealed that more than half of the data entries reviewed did not specify the probiotic strain utilized. Sampling was conducted by randomly selecting 2–5 records of patents and clinical trials, respectively, for each of the top 24 most frequently studied infectious diseases. The number of patents and clinical trials sampled for each infectious disease was contingent upon the number of results included in the final dataset to enhance sample accuracy, comprising approximately 10% of the data. Among the 80 sampled patents, approximately 49% (n = 39) specified one or multiple probiotic strains, while out of 62 patents, approximately 39% (n = 24) specified a probiotic strain or product with a traceable composition. The absence of specification poses a barrier in the research process, as probiotic effects can vary significantly between strains, rendering it ambiguous which probiotic strain(s) are accountable for the reported health effects disclosed in patents and clinical trials, thus impeding the replicability of probiotic research.

The clinical trials scrutinized in this review were primarily sponsored/executed by academic institutions, whereas patents were predominantly applied for by industrial entities. Comparison of the contributions from the three main applicant/sponsor groups (industry, academia, and government) was conducted for each indication type following methodologies outlined in prior studies. Similar distributions were observed across all nine categories of infectious diseases between the three groups of patent applicants and clinical trial sponsors. This aligns with the understanding that clinical trials offer insights into research trends, with academic entities concentrating more on fundamental research, while patents reflect market dynamics, with industrial entities prioritizing applied research and commercialization.

The International Probiotics Association (IPA) reported in 2019 that China ranked highest in sales of probiotic supplements and yoghurts, followed by the United States and Europe. Corresponding to these sales estimates, it was observed that Asia and North America were the most favored locations for clinical trials and patent applications. As outlined by Neevel et al. (2020), the location of patent applications is closely linked to anticipated profits, given the high costs associated with patent filing and maintenance. Lower-income countries were less frequently cited as locations for patent applications and clinical trials. Reid et al. (2018) noted that many individuals in these countries lack access to probiotic products. However, the IPA underscores that these populations may stand to benefit the most from probiotics, as low hygiene standards and inadequate access to clean water contribute to a surge in infectious disease prevalence.

When interpreting the findings of this study, several limitations should be taken into account. Firstly, the patenting process can span up to 18 months from application to

publication (European Patent Office, 2021), preventing definitive conclusions from the most recent data. Similarly, it is probable that the data collected in this study has been influenced by the ongoing COVID-19 pandemic, although its full impact remains uncertain. To ensure rigorous results, our research methodology underwent validation by experts in patents, clinical trials, infectious diseases, and (medical) microbiology. To conduct a comprehensive investigation of the state of the art, we opted to focus solely on a broad range of indications for probiotics, excluding pre- and postbiotics from consideration.

For future research, it would be advantageous to delve into details such as the specific strain and dosage of probiotics indicated in relevant patents and clinical trials, as well as the mechanisms of action of these probiotics. Additionally, alternative interventions targeting the gut microbiota, such as fecal microbiota transplants (FMT), which can be considered probiotics "in extremo" and have shown efficacy in restoring dysbiosis caused by C. difficile infections (Ser et al., 2021), should not be overlooked. Interestingly, the efficacy of FMT following antibiotics is hindered by the use of a multistrain probiotic (Suez et al., 2018), emphasizing the necessity for further investigation into strain-specific effects (Hill et al., 2014).

Conclusion.

The escalating volume of research evidenced by the proliferation of patents and clinical trials over the past two decades underscores the recognition of probiotics' potential in managing infectious diseases. This aligns with reported research priorities, anticipated sales, and market growth (van den Nieuwboer et al., 2016; International Probiotics Association, 2019). Nevertheless, evidence suggests a slowdown in research and development at the nexus of probiotic products and infectious diseases. This deceleration could be attributed to the natural evolution of technology or external factors such as regulatory constraints on probiotics research. Regardless, given the backdrop of the COVID-19 pandemic and potential future infectious disease outbreaks resulting from societal changes (Hersh et al., 2012; Zhang D. et al., 2021; Skowron et al., 2022), it is imperative to foster the advancement of state-of-the-art clinical modalities targeting infectious diseases. As previously emphasized (Larsen and van de Burgwal, 2021), such progress should account for the impact of alterations to microbial communities across ecosystems.

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