RESEARCH PAPER

Potential of scientific and biotechnological applications of *Escherichia coli* Nissle 1917: Systematic review

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Abstract

Escherichia coli Nissle 1917 (EcN) is a non-pathogenic probiotic bacterial strain, which was isolated in 1917. This bacterium naturally inhabits the human intestine and is used therapeutically in medications, such as Mutaflor, for the treatment of gastrointestinal disorders, such as ulcerative colitis, diarrhea, and diverticular disease. Objective: The aim of this study was to systematically synthesize the available evidence on efficacy, performance, and functionality described in the literature for the scientific and biotechnological applications reported for the EcN strain. Methodology: A systematic search was conducted using four databases Scopus, PubMed, Google Scholar, and Cochrane between 2021 and 2025, in accordance with the PRISMA statement. A total of 259 articles were identified, of which 21 met the inclusion and exclusion criteria. Results. The findings of this study confirm the classic probiotic efficacy of EcN and revealed expanded scientific applications, including systematic and dermal effects. In the field of biotechnology, its role as a highly manipulable microbial chassis is validated, demonstrating outstanding performance in genetic engineering for ultrasensitive biosensors, efficient bioproduction using alternative substrates, and the development of targeted therapies and probiotic vaccines. However, limitations associated with the pks genomic island were identified. Conclusions: EcN is a versatile platform with transformative potential in biomedicine and biotechnology. Its future development requires rigorously addressing safety gaps through longitudinal studies and progressing toward later-phase controlled clinical trials to consolidate its applicability.

Keywords: *Escherichia coli*; *E. coli*; probiotic; synthetic biology; drug delivery; therapeutics.
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1. Introduction

Escherichia coli Nissle 1917 (EcN) is a non-pathogenic probiotic strain whose genetic safety record positions it as a leading model organism for scientific and biotechnological applications that extend beyond its traditional gastrointestinal use [1]. It can be deployed in two main areas: as an engineered microbial chassis for the synthesis of therapeutic compounds (living therapies) and as a platform for diagnostics and biosensors. These applications leverage its rapid cellular division, well-characterized physiology, and ability to colonize specific niches, offering innovative solutions in precision medicine, industrial synthesis, and environmental monitoring [2,3].

The origin of EcN dates to 1917, when Alfred Nissle isolated it from a soldier who showed immunity to a shigellosis epidemic, initially identifying its properties against intestinal pathogens. For decades, its application was limited to the treatment and prevention of digestive disorders, including ulcerative colitis, supported by its ability to modulate the microbiota and the intestinal barrier [4,5]. The transition to a biotechnological platform began with advances in synthetic and genomic biology at the end of the 20th century, which made it possible to decode and manipulate its genome with precision. Crucial factors such as its GRAS (Generally Recognized As Safe) status, the availability of advanced genetic tools (plasmids and CRISPR/Cas), and the need for more efficient microbial production systems catalyzed this evolution.

As a result, recombinant strains of EcN were developed that demonstrated superior functionality in the targeted production of bioactive molecules in situ. For example, strains designed to secrete bacteriocins, microbial interferons, or anti-inflammatory molecules have shown significant efficacy against disease, outperforming conventional probiotics [6]. Furthermore, their engineering function as biosensors, detecting and responding to biomarkers of inflammation or toxins, has created a new paradigm in early diagnosis and targeted therapy [7].

Investigating the scientific and biotechnological potential of EcN is essential due to its dual importance as part of a response to current therapeutic limitations and as a model for transnational synthetic biology. Examination of this area allows us to face challenges

Author for Correspondence: Marcia Aranda such as the targeted administration of drugs with minimal systemic effects, the creation of rapid diagnostic systems, and the sustainable production of biocomposites [8]. The benefits extend beyond the laboratory, promising the development of personalized living therapies for complex conditions such as cancer and metabolic diseases, portable biosensors for health monitoring, and optimized cell bioreactors, which could result in lower healthcare costs and advances toward more predictive and preventive medicine [9,10].

Many reviews have been published around the world on this topic. For example, a systematic review performed by Zhang et al. in China analyzed 18 studies and concluded that EcN strains modified for the targeted release of anti-inflammatory cytokines showed a significantly higher efficacy ($p<0,01$) in most models in reducing colitis while maintaining a safety profile comparable to that of the unmodified parental probiotic strain [11]. Another review conducted by researchers at an Italian university evaluated both in vitro and in vivo studies. Among the most important findings, they highlighted that probiotics such as Escherichia coli Nissle 1917 offer benefits in gastrointestinal disorders and immunomodulation. The existence in their genome of the pathogenic pks responsible for the production of the genotoxic metabolite colibactin raises concerns about their safety, as it has been linked to DNA damage, mutations, and a possible role in the development of colorectal cancer [12]. This implies that there is a need for rigorous assessment of the risks and benefits before their therapeutic use, especially in vulnerable populations.

In another review of preclinical research and at least one clinical trial, researchers from Australia and the United States explored the mechanisms of tumor colonization by the probiotic bacterium *E. coli* EcN. The study highlighted that EcN has a remarkable ability to selectively locate and colonize tumors, which is attributed to factors such as the tumor microenvironment, immune system evasion, the anomalous properties of the tumor vasculature, and the metabolic adaptability of the bacterium [13].

Therefore, to consolidate knowledge and critically evaluate the true potential of this strain, this systematic review seeks to answer the following research question: What are the results, in terms of efficacy, performance, and functionality, of the scientific and biotechnological applications reported for *Escherichia coli* Nissle 1917? To provide a structured and reproducible answer, the overall objective of this study was to systematically synthesize the available evidence of efficacy, performance, and functionality described in the literature for applications of the EcN 1917 strain and thus establish trends, comparative advantages, and critical gaps for its future development.

2. Methodology

This study was based on a systematic review of the literature in four databases, Scopus, PubMed, Google Scholar, and Cochrane, using the following keywords: *Escherichial coli* Nissle 1917, probiotic, synthetic biology, engineered bacterium, drug delivery, live biotherapeutic, and microbiome therapeutics. The research was adapted in each database according to the inclusion and exclusion criteria established for the review of studies, using Boolean descriptors and specific filters for each database.

The identification and selection of studies was carried out between November 2025 and January 2026 by four co-authors, each working on a different database, while any doubts or discrepancies were resolved through discussion with the entire team of authors. Primary articles, full texts, clinical cases, and randomized trials published in English and Spanish between 2021 and 2026 were included. The review excluded animal studies and duplicated studies. Articles were selected in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. This flow chart allows for the identification, selection, and inclusion of articles [14]. The selected documents were then imported into Rayyan (application for managing systematic literature reviews and meta-analyses), which allowed for importing and filtering the studies efficiently.

The publications were evaluated by reviewing titles and abstracts. Any that did not meet the inclusion criteria were excluded. Subsequently, full-text articles were assessed to eliminate studies that failed to satisfy the inclusion criteria, resulting in the final set of articles included in this review.

The literature search yielded a total of 259 articles, which were distributed as follows: 47 from PubMed, using the search strategy *"Escherichia coli Nissle 1917" OR "*EcN*"*; 41 from Cochrane, using *"Escherichia coli* Nissle*"* OR "EcN*"*; 123 from Google Scholar, using *"E. coli* Nissle 1917" OR "EcN" AND "scientific applications" OR "technological applications"; and 48 from Scopus, using "*E. coli*" AND "Nissle".

After title screening, 7 duplicate articles were excluded, reducing the total to 252 records. Subsequently, 198 studies were excluded following title review, 24 after abstract screening, and 9 after full-text assessment, resulting in 21 articles included in the final analysis.

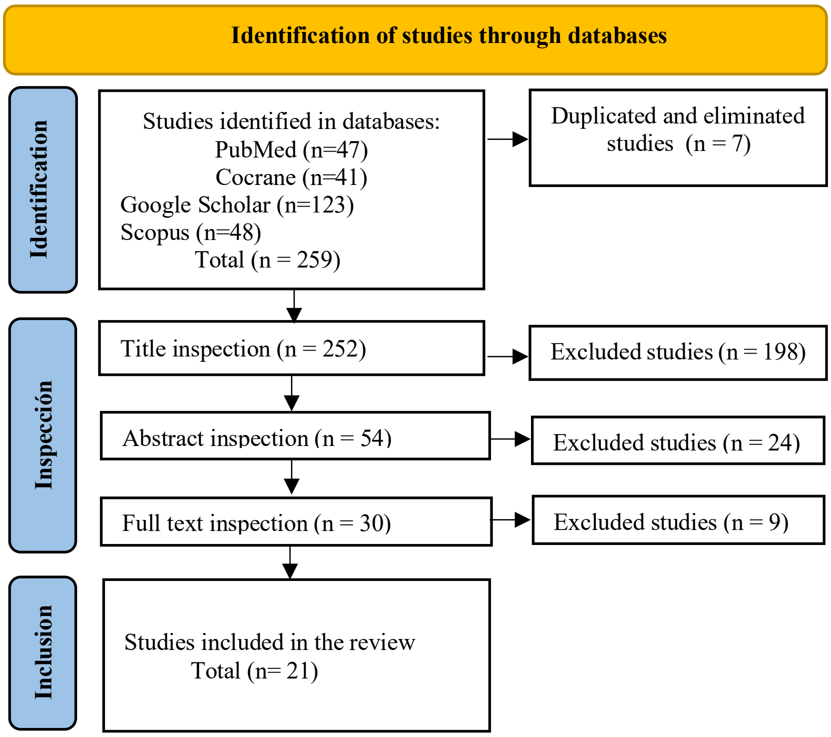

Figure 1. *Identificación, selección e inclusión de los estudios*

3. Results

3.1 Scientific applications.

Table 1 summarizes the documented scientific applications of the strain *Escherichia coli* Nissle 1917 (EcN), highlighting its efficacy, performance, and functionality across different experimental and clinical contexts. The included studies range from *in vitro* investigations to clinical trials, demonstrating EcN's ability to modulate the immune response, protect against pathogens such as Campylobacter jejuni and Pseudomonas aeruginosa, reduce inflammatory markers, improve metabolic and cognitive parameters in hepatic encephalopathy, and exhibit beneficial effects in ulcerative colitis and skin-related conditions. Additionally, distinctive properties of EcN are emphasized, including its tolerance to stress conditions, ability to form protective biofilms, and potential as a safe probiotic in neonates and adults, thereby consolidating its versatile and promising profile for biomedical and human health applications

Table 1. *Scientific applications.*

Author (Year) Country	**Title**	**Study design**	**Key findings**
Alhubail et al. (2024) UK [15]	A survey of multiple candidate probiotic bacteria…	In vitro assays evaluating EcN extracts against wound pathogens and keratinocyte protection.	EcN protected keratinocytes from *S. pyogenes* toxins and significantly reduced *P. aeruginosa* biofilm formation.
Helmy et al. (2021) USA [16]	Immuno-modulatory effect…	In vitro infection model using polarized human colonic epithelial cells exposed to *C. jejuni*.	EcN pretreatment reduced intracellular survival of *C. jejuni* and enhanced host defense activation.
Hossein et al. (2025) Iran [17]	Modulation of cytokine expression…	In vitro evaluation of EcN and OMVs in inflamed intestinal epithelial cells (HT-29).	Reduced TNF-α, IL-12, IL-1β and increased IL-10, confirming anti-inflammatory modulation.
Zhao et al. (2022) China [18]	Comparative genomic study…	Comparative genomic, transcriptomic, and metabolic analysis versus BL21(DE3) and MG1655.	Enhanced iron acquisition systems and anaerobic arginine metabolism pathways identified.
Liu et al. (2024) China [19]	Comparative biofilm characterization…	Microscopic and biochemical comparison of EcN biofilms with pathogenic strains.	Superior biofilm formation and distinct lipid composition versus O157:H7.
Manzhalii et al. (2022) Ukraine [20]	Hepatic encephalopathy treatment	Open-label randomized clinical trial (EcN vs lactulose vs rifaximin).	Improved cognitive parameters; efficacy comparable or superior

			to standard therapies; confirmed safety.
Millard et al. (2021) France [21]	Deoxyhexose sugar utilization…	Metabolic characterization under aerobic/anaerobic conditions.	Efficient utilization of L-fucose and L-rhamnose; notable 1,2-propanediol production.
Olbertz et al. (2023) Germany/Poland [22]	Benefit in term neonates	Randomized, double-blind, placebo-controlled trial (24-month follow-up).	Transient infection reduction at 4 weeks (28%); no long-term effect; safe profile confirmed.
Soo-Kyung et al. (2022) Korea [23]	Additive effect in ulcerative colitis	Multicenter, double-blind clinical trial with 5-ASA co-therapy.	Improved clinical response and endoscopic remission; maintained quality of life.
Forsyth et al. (2023) UK [24]	Decolonizing drug-resistant E. coli	In vitro model combining EcN and bacteriophages against MDR ST131.	Phage–probiotic therapy achieved sustained suppression of resistant strains.
Zandsalimi et al. (2025) Iran [25]	Anti-photoaging strategy	In vitro cellular model assessing heat-killed EcN under UVB stress.	Restored cell viability (~80%) and reduced ROS and apoptosis.

***3.2 Biotechnological applications**:*

Table 2 summarizes the biotechnological applications of *Escherichia coli* Nissle 1917 (EcN), highlighting its versatility as a platform for genetic engineering and its strong performance in the production of compounds of interest. The reviewed studies demonstrate the successful modification of EcN for advanced functions, including the design of ultrasensitive biosensors for DNA damage detection, its adaptation as a methylotrophic chassis for methanol utilization, and the stable surface expression of viral antigens—such as the HIV-1 MPER epitope—for the development of probiotic vaccines. In addition, efficient and scarless genome-editing strategies are reported, along with the functional expression of antibodies and recombinant enzymes, such as glutaminase, which enhances the functional properties of caseins, and the use of engineered strains in cancer immunotherapy (e.g., SYNB1891). Collectively, these findings underscore the potential of EcN as a safe and highly manipulable organism for applications in biodetection, bioproduction, therapeutics, and synthetic biology.

Table 2. *Biotechnological applications.*

Author (Year) Country	**Title**	**Study design**	**Key findings**
Chen et al. (2021) UK/China [26]	RecA DNA damage biosensor	Genetic circuit redesign incorporating signal amplification modules.	4.3-fold increased sensitivity to mitomycin C; improved genotoxic detection.
Chen et al. (2025) China [27]	Sucrose-utilizing EcN for heparosan	Metabolic engineering enabling sucrose assimilation for heparosan biosynthesis.	Significantly enhanced heparosan production versus glucose-based systems.
Li-Hua et al. (2025) China [28]	Methylotrophic chassis evolution	Laboratory-directed evolution for methanol/formate utilization.	Acquired methanol metabolism; efficient production of value-added compounds (e.g., 2-FL).
Ninyio et al. (2024) Sweden [29]	HIV-1 MPER surface expression	CRISPR/Cas9-mediated stable chromosomal integration of viral epitope.	High genetic stability; epitope recognized by anti-HIV antibodies.
Seco & Fernández (2021) Spain [30]	Markerless gene integration	Conjugation-based scarless chromosomal editing.	Efficient multi-gene insertion without resistance markers; controllable motility.
Gelfat et al. (2022) USA [31]	VHH-curli fusion antibodies	Surface display of VHH fused to CsgA fibers targeting virulence factors.	Neutralized Shiga toxin 2; ~75% cell viability preserved.
Liang et al. (2025) China [32]	High-throughput genomic editing	Lambda Red recombineering integrated with CRISPR (GIDGE platform).	Recombination efficiency up to 6,370 RFU/µg DNA; deletion of large genomic regions (58 kb).
Luke et al. (2024) USA [33]	SYNB1891 Phase I trial	Intratumoral administration of engineered EcN expressing STING agonist.	Activated STING pathway; induced interferon signaling; prolonged stable disease in 4 patients.
Zhao et al. (2022) China [34]	Comparative chassis analysis	Multi-omics comparison with laboratory strains.	Greater stress tolerance; lower heterologous protein expression than BL21(DE3).

Zheng et al. (2024) China [35]	Recombinant glutaminase production	Optimization of recombinant PG expression and enzyme activity assays.	49.66-fold yield increase (8.69 U/mL); improved casein solubility and foaming properties.

4. Discussion

The results reinforce the classical probiotic capacity of EcN 1917, which has been traditionally documented for gastrointestinal disorders. Studies, such as that by Helmy et al. [16], demonstrate its efficacy against Campylobacter jejuni through the activation of cellular defense mechanisms, while Hossein et al. [17] describe its ability to modulate cytokine profiles as a key mechanism underlying its anti-inflammatory action. This functionality translates into clinical efficacy, as shown in the study by Soo-Kyung et al. [23], in which EcN exhibits an additive effect in the treatment of ulcerative colitis, improving both clinical response and endoscopic remission. However, this review highlights applications that extend beyond the gastrointestinal tract, emphasizing the systemic potential of this strain. The study by Manzhalii et al. [20] demonstrates that EcN is not only safe but also effective in improving cognitive parameters in patients with hepatic encephalopathy, outperforming standard therapies such as lactulose. This finding suggests that the effects of EcN may be mediated through the gut–brain axis or via systemic modulation of metabolites, such as reducing plasma ammonia levels. Furthermore, dermatological applications [15,25] and its ability to form distinctive protective biofilms [19] open new avenues in wound care and protection against cutaneous pathogens, evidencing a functional versatility that supports its transition toward a platform with expanded biomedical applications.

In the biotechnological domain, the findings validate the concept of EcN as a highly manipulable engineered microbial chassis [10]. This review demonstrates its exceptional performance in genetic engineering, enabled by advanced and efficient genome-editing tools. For instance, Seco and Fernández [30] achieved markerless integration of multiple genes, while Liang et al. [32] developed a high-throughput genome-editing platform that allows scarless modifications, even involving large genomic fragments.

This genetic flexibility is essential for complex applications, such as the stable expression of viral epitopes on the bacterial surface for the development of probiotic vaccines [29]. The functionality of the engineered strains is equally noteworthy. EcN has been successfully designed for advanced purposes, including ultrasensitive biodetection—a DNA damage biosensor based on the RecA circuit that exhibits high sensitivity in detecting genotoxic agents [26]. Efficient bioproduction has also been achieved, as strains engineered to utilize sucrose or methanol as substrates showed enhanced production of compounds such as heparosan [27] or 2-fucosyl-D-lactose [28], respectively, highlighting their optimized metabolic performance. In addition, targeted therapeutic applications have been reported, where the surface expression of antibody domains (VHHs) on EcN effectively neutralizes toxins such as Shiga toxin [31]. Methodological and population-related factors must also be considered.

Studies reporting safety [20,22,23] primarily evaluated controlled administrations over short to medium durations in specific populations, including neonates and adults with well-defined pathologies. Under these conditions, it is plausible that the expression of colibactin is minimal or that its effects are counterbalanced by other beneficial mechanisms associated with EcN. Biological and contextual factors further suggest that genotoxic risk may be host dependent. In a healthy intestine with an intact mucosal barrier and a balanced microbiota, such a risk is considered low. However, under conditions of profound dysbiosis, chronic inflammation, or intestinal barrier damage—some of the therapeutic indications for EcN epithelial exposure and the potential procarcinogenic effects of colibactin may increase.

This review, therefore, reinforces the need, previously highlighted in the literature, to conduct rigorous risk–benefit assessments, particularly for prolonged therapies or for populations with a predisposition to intestinal damage. Hence, comparative advantages and technical limitations were assessed. Genomic and metabolic comparisons of EcN with laboratory strains, such as BL21(DE3) and MG1655 [18,34], help explain its advantages as a chassis for *in vivo* applications, including greater stress tolerance (e.g., iron limitation) and unique adaptive metabolic pathways (e.g., anaerobic arginine deaminase). However, the same study [34] also identifies a performance limitation, namely a reduced capacity for heterologous protein expression compared with BL21(DE3), a strain specifically optimized for protein production. These findings suggest that EcN is not a universal chassis but a specialized one. Its value lies not in being the most efficient producer in a bioreactor, but in serving as a safe (GRAS) and functional platform within complex environments, such as the gastrointestinal tract or the tumor microenvironment, where other strains would be unable to survive or effectively colonize.

Gaps and limitations

This review identifies significant gaps in the current literature. Longitudinal studies are required to specifically assess the risks associated with the *pks* island [12] across diverse clinical and population contexts. Despite the existence of promising preclinical and Phase I studies [33], evidence from controlled Phase II/III clinical trials remains limited, with the ulcerative colitis study [23] representing a notable exception.

Furthermore, heterogeneity in experimental designs complicates direct comparisons among different engineering strategies and limits the extrapolation of the results. Most studies focus on short-term outcomes, leaving the long-term in vivo stability of genetic modifications and the potential evolutionary trajectories of engineered strains largely unexplored.

5. Conclusions

From a scientific perspective, the evidence from the evaluated reports confirms that *Escherichia coli* Nissle 1917 (EcN) exhibits a robust and effective probiotic profile, extending beyond its traditional gastrointestinal applications to include systemic and dermatological uses. The reviewed studies demonstrate its ability to modulate immune responses, protect against intestinal pathogens such as *Campylobacter jejuni*, reduce inflammatory markers, and improve clinical outcomes in conditions including ulcerative colitis and mild hepatic encephalopathy. Collectively, these findings highlight EcN's functional versatility and support its transition from a conventional digestive probiotic to a broad-spectrum therapeutic platform.

From a biotechnological standpoint, EcN is established as an exceptionally safe and highly engineerable microbial chassis. This review highlights its successful genetic manipulation using advanced tools such as CRISPR/Cas9 and markerless integration strategies, enabling complex applications including ultrasensitive DNA-damage biosensors, efficient production of compounds such as heparosan using alternative substrates, and the stable expression of viral antigens for the development of probiotic vaccines. This optimized genetic and metabolic performance positions EcN as a promising platform for biodetection, bioproduction, and targeted therapies.

Nevertheless, this analysis also reveals critical limitations and potential risks that must be addressed. The presence of the pks genomic island, associated with the production of the genotoxin colibactin, raises concerns regarding long-term safety, particularly in vulnerable populations or in contexts of chronic inflammation. Although the included studies report a favorable safety profile under controlled, short-term administration, these concerns underscore the need for rigorous longitudinal safety studies.

Conflict of interest. The authors declare that they have no conflicts of interest.

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