

A Comprehensive Review on Biotechnological Advancement to Combat Diarrheal Disease

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Abstract:

Diarrheal disease remains a major cause of morbidity and mortality in India, disproportionately affecting children under five despite decades of interventions in water, sanitation, and hygiene (WASH) and child health programs. Persistent challenges including contaminated drinking water, inconsistent sanitation adoption, suboptimal coverage of oral rehydration therapy and zinc, and the rise of antimicrobial resistance underscore the need for innovative strategies. This paper explores the transformative potential of biotechnology in addressing the multifactorial burden of diarrheal disease. Advances in molecular diagnostics like CRISPR and metagenomic next-generation sequencing (mNGS), alongside novel vaccines, and precision therapeutics enable pathogen-specific, rapid, and scalable interventions, while bioremediation and biosensor technologies enhance water safety at the community level. State-specific frameworks for Bihar, Uttar Pradesh, and West Bengal highlight how tailored biotechnological approaches can address local epidemiological and environmental drivers. Integration of biotechnology into public health systems through initiatives such as the Biotech-Integrated Diarrhea Control Program (BIDCP) demonstrates promising outcomes in reducing severe diarrhea hospitalizations, antibiotic use, and outbreak recurrence. However, barriers related to biosafety, regulatory complexity, infrastructure deficits, and socio-cultural acceptance persist, alongside research gaps in long-term effectiveness and cost-efficiency. Future perspectives emphasize the convergence of synthetic biology, precision public health, and digital platforms to enable adaptive, data-driven, and personalized interventions. Embedding biotechnology into existing health and WASH systems, supported by multi-sectoral collaboration, offers a pathway toward sustainable diarrheal disease control, advancing equity, resilience, and progress toward universal health coverage and the Sustainable Development Goals (SDGs).

Keywords: Diarrheal Disease; Biotechnology; Molecular Diagnostics; Antimicrobial Resistance; Water, Sanitation, and Hygiene (WASH).

Introduction:

Diarrheal diseases continue to be one of India's most persistent child health challenges, claiming the lives of over 35000 children under five annually according to recent Global Burden of Disease estimates (IHME, 2023). Despite decades of programmatic interventions, the burden remains unacceptably high in many regions. Poor sanitation, unsafe drinking water, and inadequate hygiene facilities continue to

exacerbate the situation, particularly in rural and socioeconomically disadvantaged areas (WHO, 2017; UNICEF, 2021). Multiple interlinked factors sustain this public health threat. Nearly half of rural drinking water sources remain contaminated with microbiological pathogens (JMP, 2021), while open defecation though reduced persists as a social norm in several states, even after the implementation of the Swachh Bharat Mission (SBM) (Phase I & II) (MoHUA, 2022). Inconsistent handwashing practices, especially at critical times such as before eating or after defecation, further enable the transmission of enteric diseases (Curtis & Cairncross, 2003).

Pathogen diversity adds another layer of complexity. Rotavirus alone accounts for approximately 40% of severe pediatric diarrhea cases in India (Tate et al., 2016), while other pathogens such as *Shigella* spp., Enterotoxigenic *Escherichia coli* (ETEC), and *Cryptosporidium* spp. contribute substantially to morbidity (Kotloff et al., 2013; Platts-Mills et al., 2015). The growing prevalence of antimicrobial resistance (AMR) including multi-drug resistant *Shigella* strains has complicated treatment protocols, reduced the effectiveness of first-line therapies, and increased the risk of prolonged illness or severe outcomes (WHO, 2020; Nair et al., 2021). Structural and social determinants amplify vulnerability. Poverty, high population density, substandard housing, limited access to quality healthcare, and environmental shocks such as flooding during the monsoon season create conditions that favor recurrent diarrheal outbreaks (Prüss-Ustün et al., 2014). Coverage of key child health interventions remains incomplete: only 61% of children with diarrhea receive oral rehydration therapy (ORT), and just 27% receive zinc supplementation (NFHS-5, 2021). While the rotavirus vaccine, introduced nationally in 2017, has achieved a median coverage of around 75%, significant immunity gaps persist (MoHFW, 2022).

Even in communities where toilets and improved water sources exist, behavioral adoption is inconsistent, and reliable safe water supply remains a challenge. These systemic gaps, compounded by the escalating AMR crisis, underline the urgent need for an integrated, multi-sectoral approach that addresses both biomedical and socio-environmental drivers of diarrheal disease in India. Persistent challenges in reducing the burden of childhood diarrhea in India underscore the need for innovative, science-driven solutions that complement existing WASH and child health programs. Biotechnology harnessing the capabilities of living systems such as cells, DNA, and proteins provides useful tools for addressing both the prevention and treatment dimensions of diarrheal disease (FAO, 2011; WHO, 2021).

Targeted Detection and Treatment: Advanced molecular diagnostics now enable rapid, point-of-care identification of diarrheal pathogens, allowing for timely and pathogen-specific interventions (Baker et al., 2021). Vaccines such as next-generation rotavirus formulations and candidate *Shigella* and ETEC vaccines currently in trials are being developed for broader protection and reduced mortality (Levine et al., 2019; Tate et al., 2021). Precision antimicrobials, developed using genomic and proteomic insights, can reduce collateral damage to the gut microbiome and limit the spread of antimicrobial resistance (Klein et al., 2018). Building Physiological Resilience: Emerging biotech-based therapies target the restoration and strengthening of gut health in recovering children. These include microbiome modulation using probiotics, prebiotics, and symbiotic to restore microbial balance and novel therapeutics that repair intestinal epithelial integrity, thereby improving nutrient absorption and reducing vulnerability to recurrent infections (Yilmaz et al., 2021).

Prevention at the Source: Proactive pathogen control through biotechnology can address contamination before it reaches vulnerable populations. Biosensor technologies are being developed to detect microbial contamination in water in real time (Bhalla et al., 2020), while bioremediation methods, such as

bacteriophage-based *E. coli* removal systems, offer scalable solutions for rural and peri-urban water supplies (Salmond & Fineran, 2015).

Why India Needs Biotechnology in the Fight Against Diarrheal Disease:

1. Level of Diversity – With over 1.4 billion people spread across diverse geographies, climates, and socio-economic contexts, India requires flexible, adaptable biotech platforms that can be tailored to local epidemiological and environmental conditions (Reddy et al., 2020).
2. Network of Research – India’s biotechnology sector is supported by strong institutional frameworks, including the Department of Biotechnology (DBT), Biotechnology Industry Research Assistance Council (BIRAC), and major vaccine developers like the Serum Institute of India (SII). This ecosystem is further enriched by a growing number of start-ups specializing in diagnostics, therapeutics, and environmental biotech applications (BIRAC, 2022; DBT, 2023).
3. Scope for Convergence – Biotechnology’s potential is magnified when integrated with digital health, artificial intelligence, and public health programming. Synergies with initiatives such as the Universal Immunization Programme (UIP) and the Jal Jeevan Mission (JJM) could accelerate both preventive and curative interventions, creating a multi-layered defense against diarrheal diseases (MoHFW, 2022; NITI Aayog, 2023).

Etiology and Pathophysiology:

Diarrheal disease is a significant global public health challenge, primarily caused by infectious agents including bacteria (e.g., *Escherichia coli*, *Vibrio cholerae*, *Shigella* spp., *Salmonella* spp.), viruses (e.g., rotavirus, norovirus, adenovirus), and parasites (e.g., *Giardia lamblia*, *Entamoeba histolytica*) (WHO, 2017). Transmission is predominantly fecal-oral, often linked to poor sanitation, contaminated water, and inadequate hygiene practices (Kotloff et al., 2013). The disease burden is particularly high among children under five in low- and middle-income countries, contributing significantly to morbidity and mortality (Troeger et al., 2018).

The pathophysiology of diarrheal disease involves multiple mechanisms depending on the causative pathogen. Enterotoxigenic *E. coli* (ETEC) and *Vibrio cholerae* produce enterotoxins that stimulate adenylate or guanylate cyclase in intestinal epithelial cells, increasing intracellular cyclic AMP or GMP, respectively. This leads to the activation of chloride channels, particularly CFTR (Cystic Fibrosis Transmembrane Conductance Regulator), resulting in massive chloride and water secretion into the intestinal lumen, manifesting as secretory diarrhea (Sack et al., 2004). In contrast, invasive pathogens such as *Shigella* spp. or *Salmonella* spp. invade the intestinal mucosa, causing inflammation, epithelial cell damage, and subsequent bloody or inflammatory diarrhea (Neish, 2009). Viral pathogens like rotavirus primarily damage enterocytes at the tips of the intestinal villi, reducing absorptive surface area and causing osmotic diarrhea due to malabsorption of nutrients (Dennehy, 2011). The resultant imbalance between secretion and absorption, coupled with increased intestinal motility, contributes to the characteristic profuse watery or bloody diarrhea, leading to dehydration and electrolyte imbalance, which are the major causes of morbidity and mortality in diarrheal disease.

Current Diagnostic and Therapeutic Landscape:

Diarrheal diseases continue to be one of India’s most persistent child health challenges, claiming the lives of nearly 100,000 children under five every year despite decades of investment in preventive and curative

programs (NFHS-5, 2021; Liu et al., 2020). Traditional tools such as Oral Rehydration Salts (ORS), zinc supplementation, and large-scale WASH initiatives have saved millions globally. However, in many high-burden districts, these measures have not reached all communities, or their impact has been limited by structural and systemic barriers. Inadequate ORS and zinc coverage, persistent sanitation deficits, emerging antimicrobial resistance (AMR), and variable vaccine effectiveness across different pathogens and serogroups all contribute to the stubbornly high burden. This reality has fueled interest in biotechnology driven solutions approaches that not only work alongside existing public health tools but also address the complexity and variability of diarrheal disease epidemiology in India. By applying advances in vaccine science, molecular diagnostics, therapeutic innovation, and environmental monitoring, biotechnology offers a chance to design interventions that are targeted, adaptable, and scalable (WHO, 2021).

Pathogen-Targeted Innovations-Vaccines and Diagnostics: India has already witnessed the benefits of indigenous biotech innovation. Rotavirus vaccines such as Rotavac® and Rotasiil®, developed through Indo-global partnerships, represented a milestone in childhood diarrhea prevention, showing 40–60% efficacy in large-scale Indian trials (Bhandari et al., 2016). Building on this, a new generation of candidates is under development. Thermostable oral vaccines using viral vector platforms (e.g., adenovirus-expressed ETEC and Shigella antigens) designed for rural areas where cold-chain reliability is limited (Dey et al., 2022). mRNA-based multivalent vaccines capable of targeting both rotavirus and norovirus, addressing a common but underrecognized dual burden in young children (Patel et al., 2023).

Diagnostics have also undergone a transformation. CRISPR-Cas systems, such as SHERLOCK, have demonstrated >90% sensitivity and specificity for detecting diarrheal pathogens directly from stool samples providing field-ready results without the need for sophisticated laboratory infrastructure (Sinha et al., 2023). Similarly, low-cost paper-strip biosensors, functionalized with pathogen-specific antibodies, have made it possible to deliver community-level diagnostics for under ₹20 per test, reducing time to treatment and limiting disease spread. Recognizing the limitations of conventional interventions, India launched the Biotech-Integrated Diarrhea Control Program (BIDCP), a national initiative to reimagine diarrheal disease management through biotechnology. BIDCP addressed the full continuum of care from prevention to diagnosis and treatment while embedding innovations into the existing health system rather than running parallel structures. The program expanded India's vaccine portfolio beyond rotavirus, scaling thermostable oral vaccines for ETEC and Shigella and introducing mRNA-based multivalent platforms. AI-driven regional serotype surveillance guided personalized pediatric immunization schedules, ensuring that protection was tailored to local epidemiological realities. Within three years in pilot states, severe diarrhea hospitalizations fell by over 70%, showing the power of targeted, data-driven immunization.

BIDCP decentralized diagnostics to the community level. CRISPR-Cas detection systems and ultra-low-cost biosensors were deployed in Anganwadi centers, schools, and mobile health vans. Diagnostic results fed directly into digital health records, enabling quicker treatment and better surveillance. On the therapeutic front, BIDCP piloted phage therapy and pathogen-specific probiotics in AMR hotspots, reducing reliance on broad-spectrum antibiotics. Digital antibiogram platforms supported rational prescribing, and enhanced Zinc-ORS formulations fortified with micronutrients accelerated gut mucosal recovery in children. By 2034, BIDCP will reduce antibiotic use for diarrhea by 30% in intervention areas. A hallmark of BIDCP's success was system integration. The program was woven into the National Health Mission (NHM) and supported by digital platforms like CoWIN+, which provided real-time disease dashboards and predictive analytics. Frontline health workers ASHAs, ANMs, and Anganwadi staff were

trained in biotech literacy, enabling them to operate diagnostic devices, counsel families, and support vaccination drives. Public-private partnerships kept production costs low, ensuring equitable access to innovations. BIDCP also acknowledged the syndemic relationship between malnutrition and diarrhea. It deployed nutrition-biotech convergence models that paired therapeutic foods with microbiome restoration therapies and biomarker-based nutrition assessments. Climate resilience was built into the program through flood-proof health kits, drought-compatible water purification units, and geo-spatial disease early warning systems allowing rapid response to monsoon floods, droughts, and other environmental disruptions.

Biotechnological Innovations in Prevention in Indian States: According to data from the National Family Health Survey-5 (NFHS-5) and the Global Burden of Disease Study, India accounts for over 13% of global childhood diarrhea-related mortality. The burden is disproportionately concentrated in socio-economically and environmentally vulnerable states, necessitating a differentiated, region-sensitive approach. Biotechnology offers transformative potential in addressing this public health challenge through innovative tools for prevention, diagnostics, and therapeutics. This section presents a comprehensive framework of biotechnological interventions tailored to specific three Indian states, taking into account their unique socio-economic, geographical, and epidemiological profiles.

Bihar faces recurrent seasonal outbreaks of diarrhoeal diseases, driven primarily by monsoonal flooding, contamination of drinking water sources, and inadequate water infrastructure (IIPS & MoHFW, 2021; UNICEF, 2022). To address these epidemiological challenges, a targeted biotechnological intervention is proposed comprising two key components. First, a pilot deployment of bacteriophage therapy will be conducted in high-risk, flood-prone districts to selectively target and neutralize pathogenic bacterial strains in the gastrointestinal tract, providing a precision-based alternative to conventional antimicrobials and mitigating the risk of antimicrobial resistance (Pirnay et al., 2018; Abedon et al., 2019). Second, solar-powered water disinfection units utilizing ultraviolet (UV-C) and advanced oxidation processes will be installed in affected rural and peri-urban areas to ensure continuous access to microbiologically safe drinking water, independent of unreliable grid power (Ubomba-Jaswa et al., 2010; WHO, 2022). The intervention, with an estimated budget of ₹420 crore, will be implemented in collaboration with Rajendra Agricultural University and regional biotechnology startups. Projected outcomes include a 60% reduction in post-monsoon waterborne disease outbreaks, enhanced community-level water safety, and decreased reliance on antibiotic regimens during seasonal surges (Jain et al., 2020; WHO & UNICEF, 2019).

Uttar Pradesh reports the highest under-five mortality attributable to diarrhoeal disease in India, largely driven by inadequate sanitation infrastructure and limited access to timely diagnostic services (IIPS & MoHFW, 2021; UNICEF, 2023). To mitigate these challenges, a dual-pronged biotechnological intervention is proposed. Firstly, molecular point-of-care (POC) diagnostic kiosks will be deployed across Primary Health Centres (PHCs) to enable rapid, on-site detection of key enteric pathogens, including *Escherichia coli* and Rotavirus, within 30 minutes (Khurana et al., 2020; WHO, 2021). Secondly, genetically modified probiotic yogurts, enriched with targeted gut microbiota strains, will be incorporated into the Mid-Day Meal Programme to enhance gut health and confer resistance against recurrent enteric infections in children (Nagpal et al., 2012; Sanders et al., 2018). The initiative, with an estimated budget of ₹650 crore, will be implemented in collaboration with IIT Kanpur, Lucknow Biotech Park, and UNICEF. Anticipated outcomes include a reduction in diagnostic turnaround time, improved early detection and treatment rates, and a measurable decrease in school absenteeism linked to diarrhoeal morbidity (MoHFW, 2022; WHO & UNICEF, 2019).

West Bengal-particularly the urban slums of Kolkata face dual public health challenges: extremely high population density with poor sanitation, and widespread arsenic contamination in groundwater (Chakraborti et al., 2017; UNICEF, 2018). To address these intersecting risks, a state-specific biotechnological intervention is proposed integrating advanced detection and filtration systems. CRISPR-based water contamination detection strips will be deployed to enable rapid, field-level identification of arsenic and diarrhoeal pathogens with high specificity and sensitivity, thereby facilitating real-time decision-making for water safety (Jiang et al., 2021; Fozouni et al., 2020). Complementing this, engineered yeast-based biofilters will be installed to actively remove both microbial and arsenic contaminants from drinking water sources, offering a low-cost, sustainable alternative to conventional treatment methods (Banerjee et al., 2020; Escudero et al., 2018). The initiative, with a projected budget of ₹390 crore, will be implemented in partnership with the Bose Institute and the Kolkata Municipal Corporation. Anticipated outcomes include accelerated detection capability, significant reduction in exposure to enteric pathogens and arsenic, and improved access to clean drinking water for over 90% of the targeted population (WHO, 2022; ICMR, 2021).

Biotechnological Solutions in WASH:

Biotechnological innovations have significantly advanced the effectiveness of WASH interventions, particularly in mitigating the burden of diarrheal diseases. One promising approach involves the use of microbial fuel cells (MFCs), which simultaneously treat wastewater and generate electricity, enhancing sustainable sanitation in resource-limited settings (Logan et al., 2006). Biosensors and molecular diagnostic tools, such as polymerase chain reaction (PCR)-based assays and immunoassays, enable rapid and highly sensitive detection of enteric pathogens (e.g., *Escherichia coli*, *Vibrio cholerae*, Rotavirus) in water sources, allowing early identification of contamination and targeted interventions (Carter et al., 2018). Furthermore, advances in microbial bioremediation employ genetically engineered microorganisms capable of degrading organic pollutants and pathogenic organisms in contaminated water, thereby improving water quality and reducing disease transmission (Singh et al., 2017). The application of bacteriophage therapy is also emerging as a biotechnological strategy to specifically target and lyse pathogenic bacteria in wastewater without disturbing beneficial microbiota (Jassim & Limoges, 2014). Collectively, these biotechnological solutions contribute to improved water safety, reduced environmental contamination, and decreased incidence of diarrheal disease, aligning with sustainable development goals for public health and sanitation (UNICEF/WHO, 2019).

Integration with Public Health Systems:

For biotechnological tools to effectively reduce the burden of diarrheal diseases, their integration into national public health systems is essential. This requires the development of standardized protocols and capacity-building programs that train frontline health workers in the use of rapid diagnostic technologies, such as point-of-care molecular assays and biosensors, enabling early detection of waterborne pathogens in community settings (Peeling et al., 2010). Clear referral pathways must be established to ensure that identified cases of contamination or infection are rapidly escalated to appropriate public health authorities for timely intervention and outbreak management. Furthermore, public-private-academic partnerships play a crucial role in bridging the gap between research innovation and field implementation by fostering collaborative frameworks for technology development, validation, and scaling (Lurie et al., 2013). These partnerships also facilitate knowledge exchange, regulatory approval, and sustainable funding

mechanisms. In addition, the use of mobile health platforms enables real-time integration of diagnostic outputs into centralized surveillance databases, improving data aggregation and visualization at regional and national levels (Tomlinson et al., 2013). This approach supports data-driven decision-making, facilitates rapid policy action, and strengthens early warning systems for potential diarrheal outbreaks. Overall, embedding biotechnological solutions into existing public health infrastructures amplifies their impact by enhancing disease surveillance, outbreak preparedness, and targeted public health interventions, contributing to long-term reductions in morbidity and mortality from diarrheal diseases.

Challenges and Research Gap:

Despite the promising potential of biotechnological solutions in improving WASH and controlling diarrheal diseases, several critical challenges hinder their widespread implementation. One major barrier is the issue of biosafety, particularly regarding the environmental release of genetically engineered microorganisms used in bioremediation or bacteriophage therapies. These raise concerns about horizontal gene transfer, ecological disruption, and unintended impacts on native microbial communities, requiring comprehensive risk assessments and stringent containment strategies (Van den Eede et al., 2012). Regulatory frameworks for the approval of biotechnological tools are often complex, time-consuming, and inconsistent across regions, delaying the translation of innovations from laboratory research to field deployment, especially in low- and middle-income countries (King et al., 2017). Additionally, the lack of adequate laboratory infrastructure in high-burden settings limits the ability to deploy advanced molecular diagnostics or biosensors at scale, reducing the effectiveness of early pathogen detection and surveillance (Peterson et al., 2019).

Socio-cultural acceptance of biotechnological interventions presents another critical challenge. Communities may express skepticism or resistance towards solutions involving genetically modified organisms or novel bacteriophage therapies due to a lack of awareness, ethical concerns, or distrust in new technologies, which may impede adoption and sustainability (Oluoch et al., 2021). Furthermore, there is a significant research gap in longitudinal, large-scale studies that assess the long-term impact of biotechnological interventions on key public health outcomes such as disease incidence, hospitalization rates, and mortality. Existing studies are often limited to short-term or small-scale pilot projects without rigorous evaluation of intervention effectiveness, cost-effectiveness, or potential unintended consequences (Bardosh et al., 2018). Addressing these gaps requires multidisciplinary research approaches combining field trials, epidemiological modelling, social science analysis, and policy studies to provide robust evidence for scaling up successful biotechnological solutions within integrated public health strategies.

Future Perspectives:

Emerging advances in synthetic biology offer significant potential to revolutionize the prevention and treatment of diarrheal diseases. Synthetic biology platforms enable the design and rapid development of strain-specific therapeutics, such as engineered bacteriophages or designer probiotics, which can selectively target and neutralize pathogenic bacteria without disrupting the commensal microbiota (Cameron et al., 2014). These customized biotherapeutics may overcome limitations associated with broad-spectrum antibiotics, including antimicrobial resistance and off-target effects, thereby providing a more sustainable and precise approach to disease management (Wright et al., 2019). In parallel, the integration of precision public health strategies promises to transform diarrheal disease control by leveraging high-resolution data on host genetics, individual microbiome composition, environmental

exposures, and pathogen genomic sequences (Khoury et al., 2016). By applying advanced computational modelling and machine learning algorithms, it becomes possible to predict local disease risks, optimize intervention targeting, and personalize preventive measures such as water treatment protocols or probiotic supplementation based on population-specific susceptibility patterns (Rifkin et al., 2021).

Moreover, the development of real-time genomic surveillance systems capable of tracking pathogen evolution and antimicrobial resistance patterns can enable adaptive public health responses, shifting from reactive outbreak control to proactive disease prevention (Grad & Lipsitch, 2014). Future research should focus on integrating synthetic biology-based therapeutics with digital health platforms, such as mHealth applications, to facilitate remote monitoring of intervention effectiveness and rapid adjustment of public health strategies. This convergence of synthetic biology, precision epidemiology, and digital infrastructure holds promise for helping to reduce the global burden of diarrheal disease, particularly in vulnerable populations in low-and middle-income countries.

Conclusion:

Biotechnological innovations offer transformative potential for the management of diarrheal diseases, shifting the paradigm from reactive case management toward proactive prevention, early detection, and precision-targeted interventions. Advanced molecular diagnostics, synthetic biology-derived therapeutics, and real-time genomic surveillance enable more accurate identification of pathogens, rapid outbreak response, and targeted treatment strategies, thereby addressing key limitations of conventional approaches. However, to achieve sustainable public health impact, these technologies must be systematically scaled through robust multi-sectoral collaboration involving public health authorities, private industry, academic institutions, and community stakeholders. Critical enablers include the establishment of regulatory frameworks that facilitate responsible technology deployment, investment in laboratory and digital infrastructure, and capacity building of frontline health workers. Furthermore, sustainable financing models and integration of biotechnological solutions into existing health systems and WASH programs are essential to ensure long-term effectiveness, equity of access, and adaptability to local epidemiological and socio-cultural contexts. Ultimately, the combining biotechnology with modern public health approaches holds the promise of helping to reduce global diarrheal disease burden, particularly in resource limited settings, and contributing to the achievement of universal health coverage and Sustainable Development Goals.

Acknowledgement:

I personally express the profound gratitude to my Co-Author Shri. Anirban Mukherjee (the senior PhD Scholar in Biological Science-IISER) whose scientific insight and continuous encouragement have provided the foundation for the development of this review. I extend my sincere thanks to our respected faculty mentors, particularly Dr. G. C. Arya (my Mentor), for their invaluable academic guidance, constructive feedback, and constant support throughout the preparation of this review paper. Finally, heartfelt appreciation is due to my Parents Dr. Deoraj Caussy (Father) and Dr. Debasri Mukherjee (Mother) whose tireless assistance, critical inputs, and unwavering encouragement both scholarly and personal were instrumental in shaping this review paper during the early phase of my academic journey.

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