Process For Production Of High Molecular Weight Hyaluronan In A Recombinant Lactococcus Lactis Using Acetate Co-utilization Fed-batch Strategy

IITM Technology Available for Licensing

Problem Statement

- Current methods for **hyaluronic acid (HA)** production suffer from limitations like lower molecular weights, **hindering effectiveness** in biomedical applications.
- Existing **metabolic engineering** approaches focus on enzyme-coding genes but often overlook **crucial cofactors**, impacting HA production in recombinant strains like **L. lactis**.
- Traditional methods and past engineering efforts left an **unmet need** for higher molecular weight **HA demand** in **medical applications**.
- Utilization of **cost-effective acetate** in HA production faces challenges, there is a **critical gap** in exploring **cofactor** engineering strategies to enhance **HA production** and achieve greater stability for biomedical uses.
- Hence, there lies a need for enhancing **MWHA production,** using process strategies, especially with acetate supplementation and co-utilization.
- The instant invention discloses a **process** for **producing higher MWHA (3.4 MDa)** with **high yield** by anaerobic microbial fermentation with process control parameters.

Technology Category / Market

Biotechnology & Genetic Engineering

Industry: Pharmaceuticals, Biomedical Products

Applications: Advanced Materials, Food & Drugs, Medical & Surgical, Medical-grade hyaluronic acid (HA) for visco-supplementation in osteoarthritis treatment, High MWHA for enhanced stability in eye surgeries, HA in wound healing applications, HA for anti-cancer drug delivery, Cosmetic applications utilizing low molecular weight HA.

Market: The Global Hyaluronic Acid Market was estimated at **USD 1.1 Bn in 2021,** is expected to reach around **USD 2.60 Bn by 2030**, growing at **8% CAGR from 2022 to 2030.**

Research Lab

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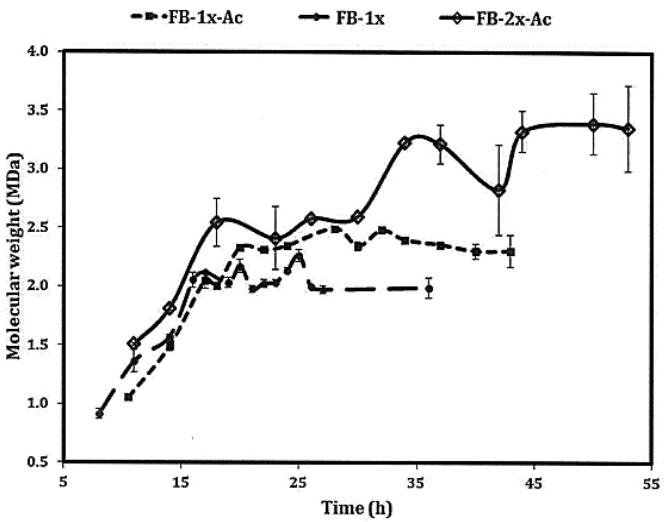
Problem Statement

The invention introduces a **process** for producing **hyaluronic acid (HA)** with a consistently high molecular weight **(3.4 MDa)** through **anaerobic microbial fermentation**. The process comprises:

- Utilization of a genetically engineered strain of Lactococcus lactis, named **MKG6**, expressing key genes from Streptococcus zooepidemicus for **enhanced HA biosynthesis**.
- **Strategically manipulating metabolic pathways** (**FIG 2**) and introduces acetate co-utilization to optimize cofactors like acetyl-CoA, crucial for HA production.
- **Incorporating** batch acetate pulse feed, batch process with acetate and glucose pulse feed, constant fed-batch, and pH feedback fed-batch strategies for **controlled** & **sustained HA production.**

FIG 1 illustrates Thermo-gravimetric analysis of Hyaluronic acid.



Intellectual Property

IITM IDF No.: **1862** | IP No.: **412658 (Granted)**
PCT Application No. PCT/IN2020/050447

TRL (Technology Readiness Level)

TRL-4: Validated in Laboratory

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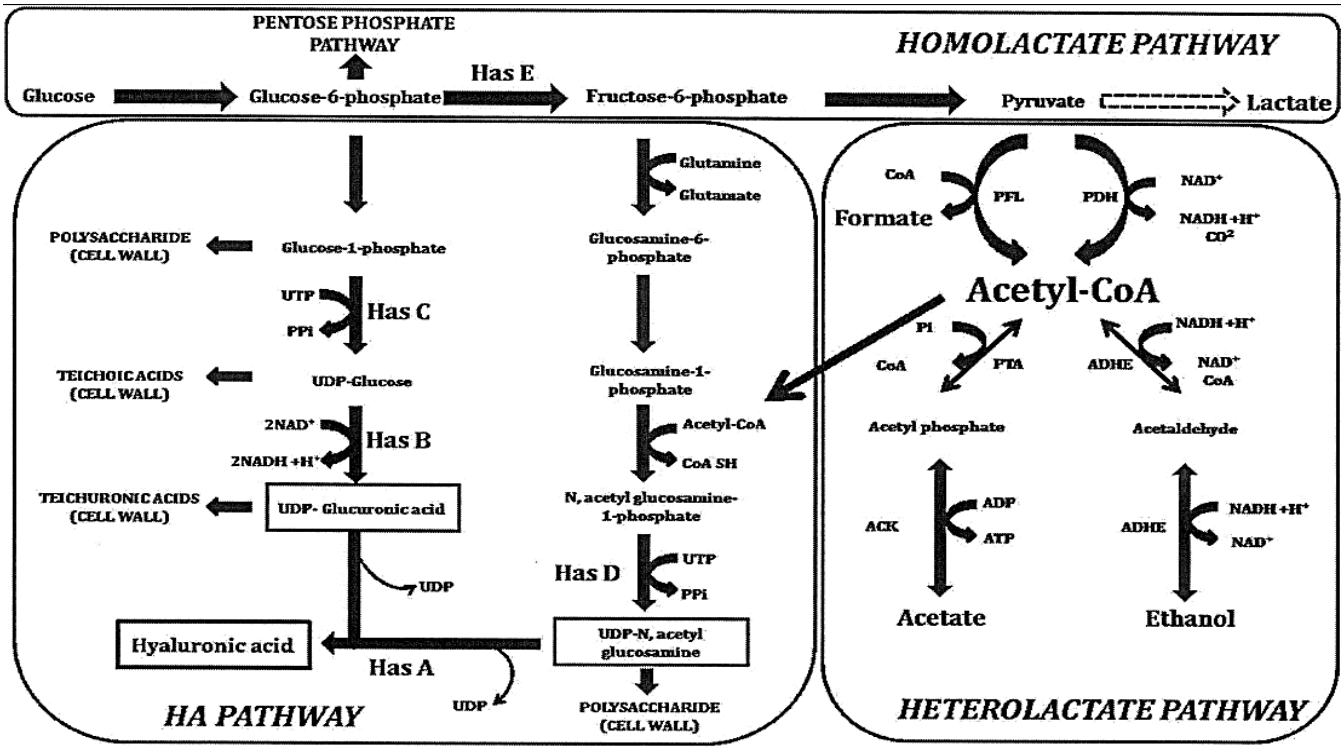
Industrial Consultancy & Sponsored Research (IC&SR)

Key Features / Value Proposition

User perspective:-	Enhanced Product Efficacy, Improved product Stability which is critical for reliable outcomes in medical treatments.
	Versatile Applications, including osteoarthritis treatment, eye surgeries, wound healing, anti-cancer drug delivery, and cosmetics.
	Biocompatibility with reduced immunogenicity and non-toxicity. Advanced Healthcare Solutions for various medical conditions.
Industrial perspective:-	Cost-Effective Production, Breakthrough Technology achieving MWHA of 3.4 MDa.
	Market Leadership and Bioprocessing Innovation with novel fermentation strategies.
	Implement advanced fed-batch fermentation processes, including acetate pulse feed and pH feedback, for sustained high MWHA.
Technology perspective:-	Employ cutting-edge genetic engineering techniques for recombinant L. lactis MKG6, enhancing HA pathway expression.
	Strategically manipulate metabolic fluxes to maximize precursor availability and HA production. Introduce acetate co-utilization to optimize acetyl-CoA levels, a key cofactor in HA biosynthesis.
	Leverage in-silico flux balance analysis to understand and optimize intracellular fluxes, influencing HA production.

Figure 2: Hyaluronic Acid Biosynthetic Pathway in L. lactis



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