**ABSTRACT**

Therapeutic enzymes are proteins which can be used to treat rare and deadly diseases. They represent a small but profitable market. Therapeutic enzymes are superior to non-enzymatic drugs owing to their high specificity toward the target and also their ability to multiple substrate conversion. They are essential for speeding up all the metabolic processes and many a life-supporting chemical inter-conversions. Actinomycetes including *Arthrobacter* form an enormous reservoir of secondary metabolites and enzymes. The characterization of L-asparaginase, β-glucosidase, urate oxidase, methionine γ-lyase, acetyl cholinesterase, and arginase activities from actinomycetes *Arthrobacter* clearly demonstrate the potential of *Arthrobacter* as potent producer of therapeutic enzymes. These metabolic enzymes can be used either separately or in combination with other therapies for the treatment of several diseases such as leukemia, gout, asthma, and neurological disorders. The objective of this review is to compile the information on the application of therapeutic enzymes produced by *Arthrobacter* and their future prospects as drugs.

**KEYWORDS:** Actinomycetes, *Arthrobacter*, Diseases, Therapeutic enzymes, Therapies

**INTRODUCTION**

Among new drug substances, the use of proteins as pharmaceuticals is steadily increasing [1]. Microbes contribute to the production of the majority of commercially important bioactive compounds. The microorganisms have proved to be very efficient and economical source of therapeutic enzyme and are preferred over plants and animals, owing to their economic cultivation, stability, flexibility in process modification and optimization. All these characteristics facilitate the large-scale microbial production of enzymes [2]. Actinomycetes are widely distributed in the earth’s ecosystem and are the most potent resource of biotechnological and pharmaceutical studies [3]. Previous studies conducted on actinomycetes were directed mainly on antibiotic production, only a few reports citing the potential of actinomycetes for the production of enzymes have been listed.

Microbial isolates belonging to genus *Arthrobacter* are a notable source for the production of therapeutic enzymes. The *Arthrobacter* genus constituted by Conn and Dimmick [4] consisting of more than 84 species exhibiting high G+C content ranging from 59 to 66 mol% [5]. The species of *Arthrobacter* genus are most prevalent amongst soil bacteria. The member species of genus *Arthrobacter* are Gram-positive and obligate aerobes. They form a soft and smooth colony which is yellow to white in coloration [6, 7]. They undergo rod-coccus growth cycle. However, some members of the genus are spherical in shape, occurring in pairs and tetrad similar to *A. agilis* [4]. *A. atrocyaneus*, *A. citrus* and *A. simplex* exhibit mobility initially, but become non-mobile after attaining coccoid morphology [8]. The *Arthrobacter* genus is metabolically versatile producing many different enzymes and are also resilient to undesirable environmental conditions. They are prolific sources of medically important enzymes with multifarious applications. They are also used in the bioremediation of groundwater contaminated with pesticides and herbicides [9]. *Arthrobacter* sp. genera serve as bioindicators of contaminated habitats and also act as agents for bioremediation of contaminants, mostly by facilitating the synthesis of proteins for cellular survival [10].

The application of microbial enzymes as the drug is an important aspect of the present-day pharmaceutical industry. A very high degree of purity is needed for therapeutic enzyme preparations. Usually, enzymes with low $K_m$ and high $V_{max}$ value are selected because of their maximal efficiency even at a very low concentration of enzyme and substrate. Thus, the selection of sources for the production of such enzymes is crucial [2]. A number of medically useful enzymes have been reported from genus *Arthrobacter*. Subsequently, isolates of *Arthrobacter* genus gained much attention of researchers. Taking into consideration the importance of therapeutic enzymes, the enzymes produced by the members of the genus *Arthrobacter* can be classified into three categories. These are pharmaceutical enzymes where the protein directly acts as the therapeutic agent, prodrug-activating enzymes where the protein indirectly results in a clinical effect and diagnostic enzymes where the protein is highly selective and specific to target and provide indirect results in a clinical effect and diagnostic enzymes where the protein is highly selective and specific to target and provide

**Fig. 1:** Schematic illustration of different therapeutic enzymes reported from *Arthrobacter* sp

**Therapeutic enzymes producing Arthrobacter** sp. of terrestrial origin

Soil represents a promising habitat for discovering and isolating new natural products, and only<1% of soil bacterial species are...
currently known [11]. The *Arthrobacter* genus is an indigenous flora of soil and usually consists of an important section of the rhizosphere microflora. A key characteristic of *Arthrobacter* is their nutritional versatility with simple nutritional needs together with the ability to exploit a number of compounds as a source of carbon and nitrogen. The main features of *Arthrobacter* held responsible for their prominent ecological presence in arid soils are the minimum growth rate, the rapid decrease in endogenous metabolism, the accumulation of a considerable amount of reserve material, the high resistance to desiccation in soil, the small spherical shape of cells and the long survival times during starvation [12].

Cold-active β-galactosidase producing *Arthrobacter* sp. SB has been reported from Antarctic soil samples. This enzyme has an optimal growth temperature of 15-20 °C at pH 7.0 and a subunit molecular mass of 114 kDa. It is specific for lactose and not inhibited by calcium or sodium ions present in milk [13]. All these properties render it useful for the production of low-lactose milk for lactose intolerant people and can also be used as a supplement along with amylase, lipase, and protease in lactose intolerant people. Other species, namely *A. psychrolactophilus* F2, *Arthrobacter* sp. 32dlt, *Arthrobacter* sp. 20B and *Arthrobacter* sp. ON14 were also reported for production of cold-active β-galactosidase [14]. *Arthrobacter* sp. SD5 isolated from oil containing soil samples with lipase activity possess pharmaceutical applications. They studied medium composition and culture conditions for improved production of lipase. Olive oil (2.5%) as a carbon source, peptone (1.0 %) as a nitrogen source and Tween-80 (0.2%) as biosurfactant gave the optimal lipase yield [15]. *Arthrobacter* sp. strain PF01 obtained from Penguin feathers collected from Elephant Island, Antarctica was found to produce keratinase with potential medical use [16]. Isolated a bacterium from omphogeneric soil and feather fragments with keratinolytic activity in low temperature (5°C). *Arthrobacter* sp. strain PFI was identified based on morphological and biochemical tests and 16S rRNA sequencing. The bacterium presented optimum growth at 4 and 25 °C, but not at 37 °C. Proteolytic activity was observed at 4 and 25 °C in pH 7. AnTherapeutic enzyme producing *Arthrobacter* sp. of aquatic origin

Over billions of years, the ocean has been regarded as the origin of life on the Earth. Thereby marine microbial enzymes can offer novel biocatalyst with extraordinary properties. The best marine source of bacteria is sediment and also reported from water, sand, rocks, marine plants, mangrove sediment, and deep sediment. The psychrophilic bacterium *Arthrobacter* sp. 32c isolated from Antarctic Ocean reported to produce cold-adapted β-D-galactosidase. The enzyme is active at 4-8 °C and of molecular weight of 195 kDa and 75.9 kDa for native protein and monomer subunit respectively [17]. The lactate intolerance person is not able to metabolise lactose due to a congenital deficiency of the enzyme β-galactosidase [18]. The β-galactosidase enzyme can be used to treat lactose intolerance. The bacterium *A. oxydans* producing dextranase was isolated from sea mud samples. This dextranase was reported for removal of dental plaque and to treat dental caries [19].

An *Arthrobacter* sp. strain MAT3885 efficiently degrading chondroitin sulfate was isolated from marine environments. The optimum activity of chondroitin sulphate lyase was at pH 5.5-7.5 and 40 °C, with 10 min of reaction time. The native enzyme was found to be a monomer [20]. It has been exposed analytically that chondroitin lyases inhibit melanoma invasion, proliferation, angiogenesis and to treat invertebrate disc protrusion. It fosters the reclamation of axons of the central nervous system after injury and also help in improving keloid pathology. It is known for its anti-inflammatory action, anti-oxidant activity and biological activity like in symptomatic treatment of osteoarthritis, known for its anti-inflammatory activity, anti-oxidant activity and potent 2, 2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity [20].

Dextranase is known to prevent dental caries and repress dental plaque. Dextranase obtained from *Arthrobacter* sp. strain B7 hydrolyzed dextran and glucon from the dental plaque. Dextranase works efficiently at temperatures of about 37 °C and are widely used in medical and dental industries. It is used in oral care products like toothpaste and mouthwash for effective dental caries prevention. It is also used in the manufacturing of blood substitutes [33, 34, 35].

**Arginase** obtained from *Arthrobacter* sp. KUJ 8602 catalyses the hydrolysis of L-arginine. It involves in nutritional starvation therapy for treatment of human hepatocellular carcinoma, prostate cancer, and melanoma. In addition to anticancer activity, it was proved to be effective in the treatment of acute neurological disorders, rheumatoid arthritis and allergic asthma [36].

**Inulase II** *Arthrobacter* sp. H65-7 produces the enzyme inulase II that converts inulin into difructose anhydride (DFA). DFA is a promising nutrient for fighting osteoporosis because it helps absorption of calcium in the intestines [37, 38].

**Hyaluronate lyase** was obtained by cultivating *A. globiformis* strain A152. The optimum pH and temperature values for hyaluronate lyase activity were pH 6.0 and 42 °C, respectively [39]. It has been

L-asparaginase an important therapeutic enzyme belongs to amidase group. It accounts for about 40% of the global total enzyme sale. It is engrossed for the treatment of childhood acute lymphoblastic leukemia [25]. Its anti-leukemic effect work on the fact that tumor cells are incapable of synthesizing L-asparagine due to lack of asparagine synthesis. Administration of asparaginase depletes free exogenous L-asparagine thus left tumor cells in a state of fatal starvation [2].

Urate oxidase is an effective curative agent in gout treatment and act as a therapeutic drug to regulate uric acid levels. Urate oxidase was also used as a reagent to monitor uric acid levels in body fluids [26]. Elitek™ is commercially available intravenous dosage form of urate oxidase, which not only resolves the deposition of newly synthesized urate but also eliminates the long-standing tissue deposits [27, 28].

β-glucosidase obtained from *A. chlorophenolicus* catalyzes efficient biotransformation of major ginsenosides to highly active minor ginsenosides like F₂, Rh₂, F₃, etc. These minor ginsenosides show highly significant pharmacological activities including anti-fatigue, anti-inflammation, anti-neoplastic, anti-fatigue, anti-oxidant and anti-diabetic effects. The enzymatic transformation on these compounds is advantageous as it results in fewer byproducts, better environmental protection and higher stereo-specificity [29].

Methionine γ-lyase (MGL) is used as a drug target for contagious ailments evoked by parasitic protozoa and anaerobic periodontal bacteria. Recombinant MGL also administered to cause a decline in the concentration of methionine essential for the growth of cancer cells. MGL degrades sulphur containing amino acids to α-keto acids, ammonia and volatile thiols [30].

Acetylcholinesterase is mainly found at neuromuscular junctions where it serves to terminate synaptic transmission by hydrolyzing acetylcholine to inactive components namely choline and acetic acid. It is necessary for the conduction of impulses along the nerve and muscle fibers. It is used as a vaccine against *Dictyocaulus viviparus* and as a pretreatment drug in organophosphorus poisoning [22]. It is considered to be an important neurotransmitter in the regulation of cognitive function [31]. This enzyme regulates the acetycholine levels, an anti-inflammatory molecule associated with the inflammatory response during parasitic diseases [32].

Chondroitin lyase obtained from *Arthrobacter* sp. MAT3885 is effective in enhancing the regeneration of the central nervous system after injury and also help in improving keloid pathlogy. It is a chondroitin sulfate degrading enzyme results in production of chondroitin sulfate oligo or disaccharides which have a broad biological activity like in symptomatic treatment of osteoarthritis, known for its anti-inflammatory activity, anti-oxidant activity and potent 2, 2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity [20].

Dextranase is known to prevent dental caries and repress dental plaque. Dextranase obtained from *Arthrobacter* sp. strain B7 hydrolyzed dextran and glucon from the dental plaque. Dextranase works efficiently at temperatures of about 37 °C and are widely used in medical and dental industries. It is used in oral care products like toothpaste and mouthwash for effective dental caries prevention. It is also used in the manufacturing of blood substitutes [33, 34, 35].
successfully utilized in ophthalmic surgery and dermatosurgery. It has been applied as a local adjuvant to expand the diffusion capacity of local anesthetics, thus enhancing the analgesic efficacy and the anesthetized area, especially in the first few minutes following injection, mitigating intra and postoperative pain [40].

Cyclodextrin glycosyltransferase (CGTase) was obtained from A. myxorens isolated from paddy field soil. CGTase catalyzes cyclisation of α,1,4-glucans to produce cyclodextrins. Cyclodextrins are carrier molecules useful in pharmaceuticals for preparation of immediate release oral dosage forms. The molecular weight of the purified protein as determined by SDS-PAGE was 75kDa; purified CGTase was thermostable and stable over a wide pH range. Dissolution studies on β-cyclodextrin-irbesartan complex revealed that β-CDs form was useful in preparing immediate release oral dosage forms of the drug [41].

Table 1: Major therapeutic enzymes produced by Arthrobacter

| S. No. | Enzymes | Microorganisms | Applications | Reference |
|-------|---------|----------------|-------------|-----------|
| 1 | Acetycholinesterase | A. licus | Used as a pretreatment drug in organophosphorus poisoning and as a vaccine against Dictyocaulus viviparous | 22 |
| 2 | Aminotransaminase | Arthrobacter sp. KNK168 | Synthesis of sitagliptin and medicine for type-2 diabetes | 42 |
| 3 | Arginase | Arthrobacter sp. KUJ 8602 | Anticancer activity | 36 |
| 4 | Chitinase | Arthrobacter sp. | Antifungal agent | 43 |
| 5 | Cholesterol oxidase | A. simplex U-S 3011 | Diagnosis of arteriosclerosis and determination of serum cholesterol | 44 |
| 6 | Chondroitin lyase | Arthrobacter sp. MAT3885 | Effective against keloid pathology and in the regeneration of central nervous system after injury | 20 |
| 7 | Creatinase | A. nicotianae 23710 | Application in clinical diagnosis of renal function | 45 |
| 8 | Cyclodextrin glycosyltransferase | A. myxorens | Production of β-cyclodextrin useful in preparing immediate release oral dosage forms | 41 |
| 9 | Deaminase | A. oxydans | Used in anticancer and antibacterial therapies | 46 |
| 10 | Dehydrogenase | A. simplex 156 | Steroid drug biotransformation | 47 |
| 11 | Dextranase | Arthrobacter sp. | Dental caries-preventing agent | 34 |
| 12 | D-threonine aldolase | Arthrobacter sp. DK-38 | Production of bioactive molecules | 48 |
| 13 | Ethanolamine oxidase | Arthrobacter sp. | Detection of phosphatidylethanolamine levels in serum | 49 |
| 14 | Fibrinolytic enzyme FA-I | A. aureus strain DR-536 | Used as a thrombolytic agent | 50 |
| 15 | Hyaluronate lyase | A. globiformis A152 | Used in ophthalmic surgery and dermatosurgery | 39, 40 |
| 16 | Keratinase | Arthrobacter sp. strain PF01 | Transmissible spongiform encephalopathies treatment | 16, 51 |
| 17 | L-arabinose isomerase | Arthrobacter sp. | Produce D-tagatose which acts as a drug for anti-diabetic and obesity control | 52 |
| 18 | L-asparaginase | A. kerguveliensis VL-RK_09 | Antileukemic effect | 25 |
| 19 | Levanfructo-transferase | A. ureafaciens K2032 | Production of DFA IV, which act as a low-calorie sweetener, inhibit tooth decay, increase mineral absorption | 53 |
| 20 | Lipase | Arthrobacter sp. MTCC 5125 | Resolution of chiral drugs and their intermediates | 54 |
| 21 | Methionine γ-lyase | Arthrobacter sp. | Anti-parasitic and anti-cancer effects | 30 |
| 22 | N-acetyl-D-homoserine lactonase | Arthrobacter sp. IBN110 | Block quorum sensing | 55 |
| 23 | Oxidoreductases | Arthrobacter sp. | Production of enantiomerically pure alcohols | 56 |
| 24 | Penicillin acylase | A. viscous ATCC15294 | Production of semisynthetic penicillins | 57 |
| 25 | Protease | A. lutes | Potential target for developing therapeutic agents against fatal diseases such as cancer and AIDS | 58, 59 |
| 26 | Serine hydroxymethyltransferase | Arthrobacter sp. | Produce L-serine which is used to treat hereditary sensory, autonomic neuropathy type 1 | 60, 61 |
| 27 | Tyramine oxidase | Arthrobacter sp B-0813 | Diagnosis of Leucine aminopeptidase activity in serum | 62 |
| 28 | Urate oxidase | A. globiformis FERM BP-360 | Gout treatment and detection of uric acid in serum | 63 |
| 29 | Xanthine oxidase | Arthrobacter sp. | Used in amperometric biosensors for detection of xanthine and hypoxanthine | 64 |
| 30 | β-1,3-glucanase | Recombinant A. lutes | Paratransgenic control of Chagas disease | 65 |
| 31 | β-galactosidase | A. psychrotolerans | Production of low lactose milk for treatment of hypolactasia | 66 |
| | β-glucosidase | A. chlorophenolicus | Produce active minor ginsenosides having anti-neoplastic, anti-fatigue, anti-oxidant and anti-diabetic effects | 29 |

CONCLUSION

The member species of Arthrobacter genus have evolved as a group with vast metabolic and genomic diversity. Attempts should be aimed to explore the potential of Arthrobacter sp. as a source to produce novel therapeutic enzymes. The results of research on the use of Arthrobacter group for the production of therapeutic enzymes targeting various diseases have been presented. Although, symbolic progress in the discovery of different medically important enzymes has been conducted, but their large-scale commercial production is yet to be worked out. Purification is the primary step in the processing of therapeutic enzymes. Successful reports on medically important enzymes from terrestrial and aquatic Arthrobacter are available, but their commercial production conditions are yet to be investigated. In order to generate therapeutic enzymes as commercial products, different biosynthetic pathways need to be analyzed, then respective genes should be metabolically engineered, cloned into the desired host and bioprocess parameters have to be optimized.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

The authors have declared that no conflict of interest exists.

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