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Review Article

ARTHROBACTER AS BIOFACTORY OF THERAPEUTIC ENZYMES

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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

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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. citreus* and *A. simplex* exhibit mobility initially, but become non-motile after attaining coccoid morphology [8]. The *Arthrobacter* genus is metabolically versatile producing many different enzymes and 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 merit over available analytical methods (fig. 1). The information on the application of medically important enzymes produced by the members of the genus *Arthrobacter* is compiled in this review to explore the future prospects of these therapeutic enzymes as drugs.

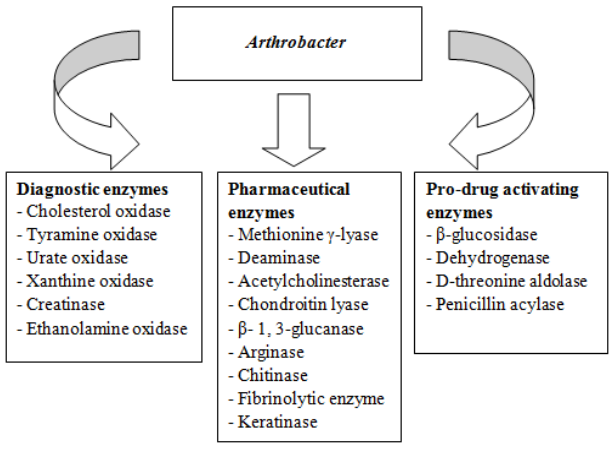

Fig. 1: Schematic illustration of different therapeutic enzymes reported from *Arthrobacter* sp

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 spheroidal 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. 32cB, *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, Antartica was found to produce keratinase with potential medical use [16]. Isolated a bacterium from ornithogenic soil and feather fragments with keratinolytic activity in low temperature (5°C). Arthrobacter sp. strain PF1 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 an

Therapeutic 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 psychrotrophic 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 lactose 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 plague 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 invertebral disc protrusion. It fosters the reclamation of axons of the central nervous system after injury [21]. The bacterium *A. ilicis* isolated from the marine sponge *Spirastrella* sp. produces extracellular serine-type acetylcholinesterase. The maximum activity of acetyl cholinesterase was found at pH 8.0 and 45 °C [22]. *Arthrobacter* sp. strain TAD20, a chitinolytic organism, was isolated from the sea bottom along the Antarctic ice shell. The bacterium secretes two major chitinases, ChiA and ChiB in response to chitin induction [23]. These chitinases exhibit medical functions like elicitor action and anti-tumor activity and to treat human diseases like asthma [24].

Production of enzymes with biomedical applications by *Arthrobacter*

The major therapeutic enzymes produced by *Arthrobacter* along with their applications have been presented in table 1.

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 antileukemic effect work on the fact that tumor cells are incapable of synthesizing L-asparagine due to lack of aspartate-ammonia ligase activity. 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 F_2, Rh_1,F_1, 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 viviparous* 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 acetylcholine 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 pathology. 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 action, anti-oxidant activity and potent 2, 2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity [20].

Dextranase is known to prevent dental caries and repress dental plague. Dextranase obtained from *Arthrobacter* sp. strain B7 hydrolyzed dextran and glucan from the dental plague. 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

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. mysorens* 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	Acetylcholinesterase	*A. ilicis*	Used as a pretreatment drug in organophosphorus poisoning and as a vaccine against *Dictyocaulus viviparous*	22
2	Amine transaminase	*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. mysorens*	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. aurescens strain DR-536*	Used as a thrombolysis 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. kerguelensis* 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-acylhomoserine lactonase	*Arthrobacter* sp. IBN110	Block quorum sensing	55
23	Oxidoreductases	*Arthrobacter* sp.	Production of enantiomerically pure alcohols	56
24	Penicillin acylase	*A. viscosus* ATCC15294	Production of semisynthetic penicillins	57
25	Protease	*A. luteus*	Potential target for developing therapeutic agents against fatal diseases such as cancer and AIDS	58, 59
26	Serine hydroxymethyl-transferase	*Arthrobacter* sp.	Produce L-serine which is used to treat hereditary sensory, autonomic neuropathy type 1	60, 61
26	Tyramine oxidase	*Arthrobacter* sp B-0813	Diagnosis of Leucine aminopeptidase activity in serum	62
27	Urate oxidase	*A.* globiformis FERM BP-360	Gout treatment and detection of uric acid in serum	63
28	Xanthine oxidase	*Arthrobacter* sp.	Used in amperometric biosensors for detection of xanthine and hypoxanthine	64
29	β-1, 3-glucanase	Recombinant *A. luteus*	Paratransgenic control of Chagas disease	65
30	β-galactosidase	*A. psychrolactophilus*	Production of low lactose milk for treatment of hypolactasia	66
31	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 author have contributed equally

CONFLICTS OF INTERESTS

The authors have declared that no conflict of interest exists

REFERENCES

1. Sakarkar DM, Kshirsagar RV, Tadavi SA, Pawde PK. Tableting compression behaviour of enzyme trypsin-chymotrypsin. Int J Appl Pharm 2009;1:30-43.
2. Mane P, Tale V. Overview of microbial therapeutic enzymes. Int J Curr Microbiol Appl Sci 2015;4:17-26.
3. Bull AT. Microbial diversity and bioprospecting. ASM Press: Washington DC; 2004. p. 496.
4. Conn HJ, Dimmick I. Soil bacteria similar in morphology to *Mycobacterium* and *Corynebacterium.* J Bacteriol 1947;54:291-303.
5. Kiran S, Swarnkar MK, Pal M, Thakur R, Twari R, Singh AK, *et al.* Complete genome sequencing of protease-producing novel *Arthrobacter* sp. strain IHBB 11108 using PacBio single-molecule real-time sequencing technology. Genome Announc 2015;3:1-2.
6. Mullakhanbhai MF, Bhat JV. Morphogenesis in *Arthrobacter* species. Proc Ind Acad Sci 1967;65:231-7.
7. Holt JG, Krieg NR, Sneath PHA, Stanley JT, Williams ST. Bergey's manual of determinative bacteriology. 9th ed. Baltimore: Williams and Wilkins; 1994.
8. Stanlake GJ, Clark JB. Motility as a morphogenic character in the genus *Arthrobacter*. J Bacteriol 1976;127:1524-8.
9. Mongodin EF, Shapir N, Daugherty SC, DeBoy RT, Emerson JB, Shvartzbeyn A, *et al.* Secrets of soil survival revealed by the genome sequence of *Arthrobacter aurescens* TC1. PLoS Genet 2006;2:2094-106.
10. Chauhan A, Pathak A, Jaswal R, Edwards B, Chappell D, Ball C, *et al.* Physiological and comparative genomic analysis of *Arthrobacter* sp. SRS-W-1-2016 provides insights on niche adaptation for survival in uraniferous soils. Genes 2018;9:31-50.
11. Powthong P, Sripean A, Suntornthiticharoen P. Screening of active antimicrobial and biological enzymes of microbial isolated from soil in Thailand Pannapa. Asian J Pharma Clin Res 2017;10:73-8.
12. Cacciari I, Lippi D. *Arthrobacters*: successful arid soil bacteria: a review. Arid Soil Res Rehabil 1987;1:1-30.
13. Coker JA, Brenchley JE. Protein engineering of a cold-active-galactosidase from *Arthrobacter* sp. SB to increase lactose hydrolysis reveals new sites affecting low-temperature activity. Extremophiles 2006;10:515-24.
14. Pawlak A, Wicka M, Krajewska E. β-galactosidases from a psychrotolerant *Arthrobacter* isolates and their potential use. Pi J 2013;3:42-6.
15. Peng R, Lin W. Optimization of lipase production from *Arthrobacter* sp. SD5. Adv Mater Res 2013;791-3:116-9.
16. Ferrareze PAG, Vailati VH, Petry MV, Brandelli A, Medina LFC. Characterization of antarctic keratinolytic *Arthrobacter* sp. Ann Act Rep 2015;11:68-70.
17. Hildebrandt P, Wanarska M, Kur J. A new cold-adapted β-D-galactosidase from the antarctic *Arthrobacter* sp. 32c-gene cloning, overexpression, purification, and properties. BMC Microbiol 2009;9:151-60.
18. Huidrom S, Singh RK, Chaudhary V. Bacteriotherapy: a novel therapeutic approach. Int J Curr Pharma Res 2016;8:12-6.
19. Wang D, Lu M, Wang X, Jiao Y, Fang Y, Liu Z, *et al.* Improving stability of a novel dextran-degrading enzyme from marine *Arthrobacter oxydans* KQ11. Carbohydr Polym 2014;103:294-9.
20. Kale V, Friojonsson O, Jonsson JO, Kristinsson HG, Omarsdottir S, Hreggviosson GO. Chondroitin lyase from a marine *Arthrobacter* sp. MAT3885 for the production of chondroitin sulfate disaccharides. Mar Biotechnol 2015;17:479-92.
21. Linhardt RJ, Avci FY, Toida T, Kim YS, Cygler M. CS lyases: structure, activity, and applications in analysis and the treatment of diseases. Adv Pharmacol 2006;53:187-215.
22. Mohapatra BR, Bapuji M. Characterization of acetyl-cholinesterase from *Arthrobacter ilicis* associated with the marine sponge *Spirastrella* sp. J Appl Microbiol 1998;84:393-8.
23. Lonhienne T, Mavromatis K, Vorgias CE, Buchon L, Gerday C, Bouriotis V. Cloning, sequences and characterization of two chitinase genes from the antarctic *Arthrobacter* sp. strain TAD20: isolation and partial characterization of the enzymes. J Bacteriol 2001;183:1773-9.
24. Hamid R, Khan MA, Ahmad M, Ahmad MM, Abdin MZ, Musarrat J, *et al.* Chitinases: an update. J Pharm Bio Allied Sci 2013;5:21-9.
25. Muvva V, Munaganti RK, Indupalli MD. Studies on optimization of L-asparaginase production by *Arthrobacter kerguelensis* VL-RK_09 isolated from mango orchards. Int J Pharm Pharm Sci 2015;7:112-5.
26. El-Naggar NEA. Isolation, screening, and identification of actinobacteria with urate oxidase activity: statistical optimization of fermentation conditions for improved production of urate oxidase by *Streptomyces rochei* NEAE-25. Int J Pharmacol 2015;11:644-58.
27. Dwivedi H, Agrawal K, Saraf SA. Screening of urate oxidase producing microorganisms and urate oxidase estimation: a simple and novel approach. Int J Pharm Pharm Sci 2012;4:422-4.
28. Newcombe DS. Gout: basic science and clinical practice. Springer, Heidelberg; 2012. p. 356-7.
29. Park MK, Cui CH, Park SC, Park SK, Kim JK, Jung MS, *et al.* Characterization of recombinant β-glucosidase from *Arthrobacter chlorophenolicus* and biotransformation of ginsenosides Rb_1, Rb_2, Rc and Rd. J Microbiol 2014;52:399-406.
30. Sato D, Nozaki T. Methionine gamma-lyase: the unique reaction mechanism, physiological roles and therapeutic application against infectious diseases and cancers. IUBMB Life 2009;61:1019-28.
31. Sumithra M, Arunachalam G, Chitra V, Gowri K. Neuroprotective effect of *Sargassum ilicifolium* turner C. Agardh on acetylcholinesterase activity and attenuation of scopolamine-induced amnesia in rodents. Asian J Pharma Clin Res 2016;9:93-6.
32. Silva AD, Bottari NB, Carmo GM, Baldissera MD, Souza CF, Machado VS, *et al.* Chagas disease: modulation of the inflammatory response by acetylcholinesterase in hematological cells and brain tissue. Mol Cell Biochem 2018;438:59-65.
33. Baktir A, Zaini NC, Murdiyatmo U, Kuntaman. The potency of dextranase from *Arthrobacter* sp. strain B7 as dental plaque removal. Catatan Penelitian 2005;12:162-6.
34. Jiao YL, Wang SJ, Lv MS, Jiao BH, Li WJ, Fang YW, *et al.* Characterization of a marine-derived dextranase and its application to the prevention of dental caries. J Ind Microbiol Biotechnol 2014;41:17-26.
35. Ren W, Cai R, Yan W, Lyu M, Fang Y, Wang S. Purification and characterization of a biofilm-degradable dextranase from a marine bacterium. Mar Drugs 2018;16:51-67.
36. Unissa R, Sudhakar M, Reddy ASK. A review of biochemical and therapeutic aspects of arginase. Int J Life Sci Pharma Res 2014;4:72-97.
37. Yokota A, Hirayama S, Enomoto K, Miura Y, Takao S, Tomita F. Production of inulin fructotransferase (depolymerizing) by *Arthrobacter* sp. H65-7 and preparation of DFA III from inulin by the enzyme. J Ferment Bioeng 1991;72:258-61.
38. Tomita K, Shiomi T, Okuhara Y, Tamura A, Shigematsu N, Hara H. Ingestion of difructose anhydride III enhances absorption and retention of calcium in healthy men. Biosci Biotechnol Biochem 2007;71:681-7.
39. Zhu C, Zhang J, Li L, Zhang J, Jiang Y, Shen Z, *et al.* Purification and characterization of hyaluronate lyase from *Arthrobacter globiformis* A152. Appl Biochem Biotechnol 2016;182:216-28.
40. Buhren BA, Schrumpf H, Hoff NP, Bolke E, Hilton S, Gerber PA. Hyaluronidase: from clinical applications to molecular and cellular mechanisms. Eur J Med Res 2016;21:5-11.
41. Rajesh Y, Narayanan K, Reddy MS, Bhaskar VK, Shenoy GG, Subrahmanyam VM, *et al.* Production of β-cyclodextrin from pH and thermostable cyclodextrin glycosyltransferase, obtained from *Arthrobacter mysorens* and its evaluation as a drug carrier for irbesartan. Curr Drug Delivery 2015;12:444-53.
42. Guan L, Ohtsuka J, Okai M, Miyakawa T, Mase T, Zhi Y, *et al.* A new target region for changing the substrate specificity of amine transaminases. Sci Rep 2015;5:1-11.

43. Morrissey RF, Dugan EP, Koths JS. Chitinase production by an *Arthrobacter* sp. lysing cells of *Fusarium roseum*. Soil Biol Biochem 1976;8:23-8.
44. Kumari L, Shamsher KS. Cholesterol oxidase: role in the biotransformation of cholesterol. J Appl Biol Biotechnol 2015;3:53-65.
45. Dai J, Zhang L, Kang Z, Chen J, Du G. High-level production of creatine amidinohydrolase from *Arthrobacter nicotianae* 23710 in *Escherichia coli*. Appl Biochem Biotechnol 2015;175:2564-73.
46. Medici R, Lewkowicz ES, Iribarren AM. *Arthrobacter oxydans* as a biocatalyst for purine deamination. FEMS Microbiol Lett 2008;289:20-6.
47. Zhang H, Tian Y, Wang J, Li Y, Wang H, Mao S, *et al.* Construction of engineered *Arthrobacter simplex* with improved performance for cortisone acetate biotransformation. Appl Microbiol Biotechnol 2013;97:9503-14.
48. Liu JQ, Odani M, Dairi T, Itoh N, Shimizu S, Yamada H. A new route to L-threo-3[4-(methylthio)phenylserine], a key intermediate for the synthesis of antibiotics: recombinant low-specificity d-threonine aldolase-catalyzed stereospecific resolution. Appl Microbiol Biotechnol 1999;51:586-91.
49. Ota H, Tamezane H, Sasano Y, Hokazona E, Yasuda Y, Sakasewage S. Enzymatic characterization of an amine oxidase from *Arthrobacter* sp. used to measure phosphatidy-lethanolamine. Biosci Biotechnol Biochem 2008;72:2732-8.
50. Ming Z, Haihong H, GaoXue W. Optimization on fermentation of *Arthrobacter aurescens* strain DR-536 to secrete a novel fibrinolytic enzyme FA-I. J NWAFU Nat Sci Ed 2010;38:33-9.
51. Selvam K, Vishnupriya B. Biochemical and molecular characterization of microbial keratinase and its remarkable applications. Int J Pharm Biol Arch 2012;3:267-75.
52. Fu H, Wei Y, Zou Y, Li M, Wang F, Chen J, *et al.* Research progress on the actinomyces *Arthrobacter*. Adv Microbiol 2014;4:747-53.
53. Kim CH, Jang EK, Kim SH, Jang KH, Kang SA, Song KB, *et al.* Molecular cloning of levan fructotransferase gene from *Arthrobacter ureafaciens* K2032 and its expression in *Escherichia coli* for the production of difructose dianhydride IV. Lett Appl Microbiol 2005;40:228-34.
54. Chaubey A, Parshad R, Koul S, Taneja SC, Qazi GN. *Arthrobacter* sp. lipase immobilization for improvement in stability and enantioselectivity. Appl Microbiol Biotechnol 2006;73:598-606.
55. Park SY, Lee SJ, Oh TK, Koo BT, Yum DY, Lee JK. AhlD, an N-acyl homoserine lactonase in *Arthrobacter* sp. and predicted homologues in other bacteria. J Microbiol 2003;149:1541-50.
56. Araujo LS, Kagohara E, Garcia TP, Pellizari VH, Andrade LH. Screening of microorganisms producing cold-active oxidoreductases to be applied in enantioselective alcohol oxidation. An Antarctic survey. Mar Drugs 2011;9:889-905.
57. Ohashi H, Katsuta Y, Hashizume T, Abe SN, Kajiura H, Hattori H, *et al.* Molecular cloning of the penicillin G acylase gene from *Arthrobacter viscosus*. Appl Environ Microbiol 1988;54:2603-7.
58. Rao MB, Tanksale AM, Ghatge MS, Deshpande VV. Molecular and biotechnological aspects of microbial proteases. Microbiol Mol Biol Rev 1998;62:597-635.
59. Adamitsch BF, Karner F, Hampel W. Proteolytic activity of a yeast cell wall lytic *Arthrobacter* species. Lett Appl Microbiol 2003;36:227-9.
60. Huang J, Chen L, Hu N, Jiang W, Wu G, Liu Z. Characterization of a novel serine hydroxymethyltransferase isolated from marine bacterium *Arthrobacter* sp. and its application on l-serine production. Ann Microbiol 2015;65:1689-98.
61. Garofalo K, Penno A, Schmidt BP, Lee HJ, Frosch MP, Eckardstein AV, *et al.* Oral L-serine supplementation reduces production of neurotoxic deoxysphingolipids in mice and humans with hereditary sensory, autonomic neuropathy type 1. J Clin Invest 2016;121:4735-45.
62. Yoshino E, Matsuura K, Misaki H. Process for the production of tyramine oxidase. US 4496655 A; 1985.
63. Suzuki K, Sakasegawa SI, Misaki H, Sugiyama M. Molecular cloning and expression of urate oxidase gene from *Arthrobacter globiformis* in *Escherichia coli* and characterization of the gene product. J Biosci Bioeng 2004; 98:153-8.
64. Xin Y, Yang H, Xia X, Zhang L, Zhang Y, Cheng C, *et al.* Expression, purification and partial characterization of a xanthine oxidase (XOD) in *Arthrobacter* sp. Process Biochem 2012;47:1539-44.
65. Jose C, Klein N, Wyss S, Fieck A, Hurwitz I, Durvasula R. Recombinant *Arthrobacter* β-1, 3-glucanase as a potential effector molecule for paratransgenic control of chagas disease. Parasites Vectors 2013;6:65-73.
66. Nakagawa T, Fujimoto Y, Ikehata R, Miyaji T, Tomizuka N. Purification and molecular characterization of cold-active β-galactosidase from *Arthrobacter psychrolactophilus* Strain F2. Appl Microbiol Biotechnol 2006;72:720-5.