Multidisciplinary involvement and potential of thermophiles

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Abstract

The full biotechnological exploitation of thermostable enzymes in industrial processes is necessary for their commercial interest and industrious value. The heat tolerant and heat resistant enzymes are a key for efficient and cost-effective translation of substrates into useful products for commercial applications. The thermophilic, hyperthermophilic and microorganisms adapted to extreme temperatures (i.e, low-temperature lovers or psychrophiles) are a rich source of thermostable enzymes with broad ranging thermal properties, which have structural and functional stability to underpin a variety of technologies. These enzymes are under scrutiny for their great biotechnological potential. Temperature is one of the most critical parameters that shape microorganisms and their biomolecules for stability under harsh environmental conditions. This review describes in detail the sources of thermophiles and thermostable enzymes from prokaryotes and eukaryotes (microbial cell factories). Furthermore, the review critically examines perspectives to improve modern biocatalysts, its production and performance aiming to increase their value for biotechnology through higher standards, specificity, resistance, lowering costs, etc. These thermostable and thermally-adapted extremophilic enzymes have been used in a wide range of industries that span all six enzyme classes. Thus, in particular, target of this review paper is to show the possibility of both high value-low volume (e.g. fine-chemical synthesis) and low value-high volume byproducts (e.g. fuels) by minimizing changes to current industrial processes.

Keywords Tailor-made enzymes; Thermoadaptation for Sustainability; Genome mining for thermozymes; “Hot” acetogenesis; Green chemistry

Introduction

Some microorganisms are metabolically active in physically and geochemically extreme environments. Challenging brutal conditions trait them to expand their capabilities to grow at the physico-chemical boundaries of life such as high salt (>1.0 mol/L), low or high pH (>8.0 or < 5.0), very low at very high temperature (less than 1-15 °C or greater than 45 °C), atmospheric pressure (average 380 mmHg), >500-1200 mmHg (maximum and beyond this), very frequent high radiations, degradation of xenobiotic or recalcitrant toxic chemical, heavy and toxic metals and in the presence of inhibitors. Microorganisms growing in these hostile conditions are named ‘extremophiles’. Bacteria, Archaea and Eukarya inhabiting extreme environment have diverse cell structure, unique metabolism and ultimate survival strategies which allows them to withstand at changing unpleasant conditions viz. acidic, alkaline, haline, high temperatures, low temperatures, etc. Extremophiles capable of growth at natural and artificial high temperature environments are called ‘thermophiles’. Several extreme high temperature environments have been reported. High temperature niches on our Blue planet exists as natural habitats viz. hot springs, volcanoes, desert, solar salterns, solfataric fields, solar heated soils, fumaroles and hydrothermal vents and artificial habitats viz. compost piles, slag heap, haystacks, industrial processes, domestic laundries, solar panels, hot diaphragm of air conditioner, water heaters and refrigerators (Fig.1).

Fig.1 Natural and artificial habitats of thermophiles

Thermophiles have been isolated and identified from different high temperature environments. But, relatively little number of thermophiles are commercially exploited. Recently, novel thermophilic genera and species were isolated from different environments. Thermophiles are waiting for attention of scientist and exploit their characteristics for the benefits to mankind (Table 1). These heat loving microorganisms have inherent the ability to grow and carry out all the metabolic processes optimally at extremes. They have genetically transferable eco-physiological and functional metabolic systems, which assist them to thrive under these conditions. The thermoenzymes, important proteins and polymers produced by thermophiles are structurally stable to function in wide ranges of temperatures, and, generally, also extreme pHs and withstand the presence of high or low salt concentrations, high pressure, radiations and inhibitors (Rekadwad and Gonzalez, 2017).

Fig. 2 A number of industrial applications of thermophiles and their products in White Biotechnology

Table 1. Novel thermophiles isolated and identified from high temperature environments

Genus/Species	Strain (s)	Key feature (s)	Habitat (s)	Country	Reference
<i>Aeribacillus composti</i> sp. nov.	N.8 ^T	Found in curing step of an olive mill pomace compost sample and form cream colored colonies	Olive mill pomace compost	Italy	Finore et al. 2017
<i>Bacillus hisashii</i> sp. nov.	N-11 ^T	Isolated from Mice	Caeca of gnotobiotic mice fed with fermented compost	Japan	Nishida et al. 2015
<i>Bifidobacterium apri</i> sp. nov.	RP115 ^T	Utilize fructose-6-phosphate phosphoketolase and strictly anaerobic	Digestive tract of wild pigs	Czech Republic	Pechar et al. 2017a
<i>Brassicibacter thermophilus</i> sp. nov.	Cel2f ^T	Obligately anaerobic bacterium	Coastal marine sediment	China	Wang et al. 2015
<i>Caldovatus sediminis</i> gen. nov., sp. nov.	YIM 72346 ^T	Non-motile bacterium with predominant ubiquinone was Q-10	Hot spring, Tengchong county, Yunnan province	China	Habib et al. 2017a
<i>Caloranaerobacter ferrireducens</i> sp. nov.	DY22619 ^T	Presence of multiple peritrichous flagella	Hydrothermal field, East Pacific Ocean	China	Zeng et al. 2015
<i>Cecembia rubra</i> sp. nov.	YIM 78110	Phosphatidylethanolamine is major polar lipid	Hehua hot spring	China	Duan et al. 2015
<i>Cetia pacifica</i> gen. nov., sp. nov.	TB-6 ^T	Chemolithoautotrophic bacterium	Deep-sea hydrothermal vent	USA	Grosche et al. 2015
<i>Chloroflexus islandicus</i> sp. nov.	isl-2 ^T	Anoxygenic phototrophic non-spore forming bacterium, unbranched multicellular filaments with gliding motility	Strokkur Geyser basin	Iceland	Gaisin et al. 2017
<i>Crenalkalicoccus roseus</i> gen. nov., sp. nov.	YIM 78023 ^T and YIM 78058 ^T	Grew at pH 6.0-10.0	Alkaline hot springs, Tengchong county, Yunnan province	China	Ming et al. 2016
<i>Deferrisoma palaeochoriense</i> sp. nov.	MAG-PB1 ^T	Iron(III) reducing, anaerobic, mixotrophic	Hydrothermal vent system, Palaeochori Bay off the coast of	Greece	Pérez-Rodríguez et al. 2016

		bacterium	the island of Milos		
<i>Defluviitalea raffinosedens</i> sp. nov.	A6 ^T	Yeast extract was required for growth.	Anaerobic batch digester treating animal manure and rice straw	China	Ma et al. 2017
<i>Desulfotomaculum ferrireducens</i> sp. nov.	GSS09 ^T	Fe(III)-reduction	Composting demonstration plant, Dongguan City, Guangdong Province	China	Yang et al. 2016
<i>Desulfurobacterium indicum</i> sp. nov.	K6013 ^T	Obligate chemolithoautotroph utilize thiosulfate, sulfur and nitrate as terminal electron acceptors in the presence of H ₂ but not sulfate, sulfite nor nitrite	Sulfide sample from high-temperature hydrothermal vent in the Indian Ocean	China	Cao et al. 2017
<i>Dissulfurimicrobium hydrothermale</i> gen. nov., sp. nov.	Sh68 ^T	Sulphur utilizing bacterium	Hydrothermal pond at Uzon Caldera, Kamchatka	Russia	Slobodkin et al. 2016
<i>Dissulfurirhabdus thermomarina</i> gen. nov., sp. nov.	SH388 ^T	Sulfite-reduction	Shallow-sea hydrothermal vent, Kuril Islands	Russia	Slobodkina et al. 2016a
<i>Fervidobacterium thailandense</i> sp. nov.	FC2004 ^T	Strictly anaerobic, extremely thermophilic heterotroph	Hot spring	Thailand	Kanoksilapatham et al. 2016
<i>Galliscardovia ingluviei</i> gen. nov., sp. nov.	RP51 ^T	Utilize fructose-6-phosphate phosphoketolase	13 -month-old Hisex Brown hybrid laying hen	Czech Republic	Pechar et al. 2017b
<i>Geobacillus icigianus</i> sp. nov.	G1w1 ^T	Motile, thermophilic spore-forming strain	Hot spring of the Valley of Geysers, Kamchatka	Russia	Bryanskaya et al. 2015
<i>Geobacillus yumthangensis</i> sp. nov.	AYN2 ^T	Alkalophilic bacterium	Yumthang hot spring, North Sikkim	India	Najar et al. 2018
<i>Herbinix hemicellulosilytica</i> gen. nov.	T3/55 ^T	Cellulose-degrading bacterium	Biogas reactor	Germany	Koeck et al. 2015
<i>Herbinix luporum</i> sp. nov.	SD1D ^T	Degrade crystalline cellulose	Biogas reactor	Germany	Koeck et al. 2016a

<i>Herbivorax saccincola</i> gen. nov., sp. nov.	GGR1 ^T	Cellulolytic bacterium	Lab-scale biogas fermenter	Germany	Koeck et al. 2016b
<i>Kyrpidia spormannii</i> sp. Nov.	EA-1 ^T	Hydrogen-oxidizing bacterium	Hydrothermal systems at São Miguel Island	Portugal	Reiner et al. 2018
<i>Laceyella thermophila</i> sp. nov.	YIM 79486 ^T	Produce abundant endospores on short sporophores	Jinze hot spring in Tengchong county, Yunnan province	China	Ming et al. 2017
<i>Limisphaera ngatamarikiensis</i> gen. nov., sp. nov.	NGM72.4 ^T	Pink-pigmented Verrucomicrobia	Hot spring in the Ngatamariki geothermal field	New Zealand	Anders et al. 2015
<i>Limnochorda pilosa</i> gen. nov., sp. nov.	HC45 ^T	Facultatively anaerobic, pleomorphic bacterium	Brackish meromictic lake	Japan	Watanabe et al. 2015
<i>Marinitoga arctica</i> sp. nov.	2PyrY55-1 ^T	Possesses a polar flagellum and a sheath-like outer structure ('toga')	Hydrothermal white-smoker chimney, Soria Moria vent field, Mohns Ridge, Norwegian-Greenland Sea	Norway	Steinsbu et al. 2016
<i>Meiothermus luteus</i> sp. nov.	YIM 72257 ^T	Presence of uncharacterized phospholipid and two glycolipids	Hot spring in Tengchong county, Yunnan province	China	Habib et al. 2017b
<i>Melghiribacillus thermohalophilus</i> gen. nov.	Nari2A ^T	Filamentous	Algerian salt lake, Chott Melghir	Algeria	Addou et al. 2015
<i>Novibacillus thermophilus</i> gen. nov., sp. nov.	SG-1 ^T and SG-2 ^T	Facultative anaerobe	Saline soil sample Compost sample	China	Yang et al. 2015
<i>Petrothermobacter organivorans</i> gen. nov., sp. nov.	ANA ^T	Chemoheterotrophic, acetate-oxidizing and iron(III)-, manganese(IV)-, nitrate- and sulfate-reducing bacterium	Deep subsurface oil field	Japan	Tamazawa et al. 2017
<i>Pseudogracilibacillus endophyticus</i> sp. nov.	DT7-02 ^T	Form pinkish-yellow, opaque, glistening colony	Root of <i>Oenotherabiennis</i> (evening primrose)	Republic of Korea	Park et al. 2017
<i>Raineyia orbicola</i> gen. nov., sp. nov.	SPSPC-11 ^T	Menaquinone 7 present as major quinone	Hot spring	Portugal	Albuquerque et al. 2018
<i>Rubrobacter spartanus</i> sp. nov.	GGR1 ^T	Cellulolytic, anaerobe	Soil, Caldera of Kilauea Volcano	USA	Norman et al. 2017

			in Hawaii Volcanoes National Park		
<i>Saccharopolyspora subtropica</i> sp. nov.	T3 ^T	White aerial mycelium and colourless to pale yellow vegetative mycelium	Soil of a sugar cane field	China	Wu et al. 2016
<i>Scopulibacillus daqui</i> sp. nov.	ZQ18-1 ^T	Central oval endospores with swollen sporangia	Daqu sample, Sesame-flavour liquor-making process	China	Yao et al. 2016
<i>Tepidibacillus decaturensis</i> sp. nov.	Z9 ^T	Iron-reducing bacterium	Mt. Simon Sandstone of the Illinois Basin, Illinois	USA	Dong et al. 2016
<i>Tepidibacillus infernus</i> sp. nov.	MBL-TLPT	Selenate and arsenate respiring bacterium	TauTona gold mine	South Africa	Podosokorskaya et al. 2016
<i>Thauera hydrothermalis</i> sp. nov.	GD-2 ^T	Non-spore-forming bacterium	Hot spring in the Tibet Autonomous Region	China	Yang et al. 2018a
<i>Thermanaeromonas burensis</i> sp. nov.	IA106 ^T	Thermophilic halotolerant strain	Callovo-Oxfordian clay environment	France	Gam et al. 2016
<i>Thermoactinomyces guangxiensis</i> sp. Nov.	CD-1 ^T	Spherical-polyhedron endosphere with smooth surface	Mushroom compost	China	Wu et al. 2015
<i>Thermocrinis jamiesonii</i> sp. nov.	GBS1 ^T	Chemolithotrophic, microaerophilic bacterium	Water column of Great Boiling Spring, Nevada	USA	Dodsworth et al. 2015
<i>Thermodesulfatator autotrophicus</i> sp. nov.	S606 ^T	Sulfate-reducing bacterium	Sulfide sample, deep-sea vent chimney wall in the Indian Ocean	China	Lai et al. 2016
<i>Thermodesulfatimonas autotrophica</i> gen. nov., sp. nov.	SF97 ^T	Anaerobic, chemolithoautotrophic bacterium	Terrestrial hot spring (Kuril Islands)	Russia	Slobodkina et al. 2017b
<i>Thermostilla marina</i> gen. nov., sp. nov.	SVX8 ^T	Did not grow at atmospheric concentration of oxygen but grew microaerobically (up to 2 % oxygen in the gas phase)	Shallow submarine hydrothermal vent, Vulcano Island	Italy	Slobodkina et al. 2016b

<i>Thermosulfuriphilus ammonigenes</i> gen. nov., sp. nov.	ST65 ^T	Ammonification of nitrate	Deep-sea hydrothermal vent chimney, Eastern Lau Spreading Centre, south-western Pacific Ocean	Russia	Slobodkina et al. 2017a
<i>Thermus caldifontis</i> sp. nov.	YIM 73026 ^T	Yellow colored colonies	Hot spring in Tibet	China	Khan et al. 2017a
<i>Thermus sediminis</i> sp. nov.	L198 ^T and L423 ^T	Ability to oxidize thiosulfate and reduce arsenate	Little Hot Creek, the Long Valley Caldera	California	Zhou et al. 2018
<i>Tibeticola sediminis</i> gen. nov., sp. nov.	YIM 73013 ^T and YIM 73008 ^T	Possesses polar flagellum	Hot spring in Tibet, western Tibet province	China	Khan et al. 2017b
<i>Thermogutta terrifontis</i> gen. nov., sp. nov.	R1 ^T	Anaerobic representatives of the phylum <i>Planctomycetes</i>	Hot spring, Kunashir Island	Russia	Slobodkina et al. 2015
<i>Thermogutta hypogea</i> sp. nov.	SBP2 ^T		Deep gold mine	South Africa	

Currently the world has high demand for high value and low cost, and vice versa, organic products obtained from renewable, economic and readily available biomass. Biomolecules in bulk quantities and fine chemicals are produced in industries but the use of thermophiles is quite scarce. Thermozyms have important roles in bioconversion of raw materials or biomass into products.

Thermophiles are employed in numerous processes. Operationally stable thermophiles and thermozyms are useful in industrial processes which benefit of their functions and unique properties. Besides, high temperature processes offer process improvement, for instance, mixing, increases substrate solubility and high biomass transfer rate with a negligible risk of contamination (Gopinath et al. [2015](#)). They have a wide number of applications on various industries and processes viz. detergent, textiles, leather industry, polymerase chain reaction (PCR), ligase chain reaction (LCR), diagnostics, food, paper and pulp, dairy products, baking, brewing, amino acid production, sugar mills, acrylamide production, starch processing, fat hydrolysis, chemical synthesis, esterification, organic biosynthesis, paper bleaching, pharmaceutical, molecular sieves, surfactants for oil recovery, bioinoculants, waste treatment, textile dye treatment, bio-energy generation/biofuels, bio-filters, breast cancer treatment, bioconversion, bioremediation, hygiene indicator, for crude oil degradation, heavy metal recovery ([Fig.2](#)) and combination of former processes. In this research review, current developments and potential applications of thermophiles and thermozyms from bacteria and fungi were discussed. This review will provide with critical notions about potential thermophilic products and assists to build new future perspectives looking into a new biotechnological revolution.

Prokaryotes and eukaryotes as cell factories for thermostable biocatalysts

Today's World demands huge amounts of renewable and cheap biomass as a primary source for production of a wide variety of chemicals including fine, low-scale and high-value products, as well as bulk quantities of high-scale and low-value building blocks to be used in

biotechnology and chemical processes. These can be produced in biorefineries using sustainable bioprocesses. Now a day prokaryotic and eukaryotic microbial cells factories are employed for bioconversion of biologically originated mass into desired products. A number of bioprocesses require either whole microbial cell or its byproducts in the form of enzymes which are operationally stable at high temperature (Table 2). Therefore, processes carried out at high temperature address risk of contamination and minimize contaminants, besides high temperature process offer better substrate solubility, ensue an environment-friendly industry, facilitating mixing and substrate availability and enhance high biomass transfer and bioconversion rate. Thus, thermophilic microorganisms have attracted the microbiologist and biotechnologist due to their enormous potential and stability at high temperatures. Few thermophilic microorganisms have been so far used and a few cells have been reported as ideal for biotechnological processes as raw models with broad applicability in research and industrial processes. They would have use as genetic tools, source and finger prints of novel molecules, primary gene sequence, and functional traits, to be major players in the protein engineering field (Verma and Kanwar 2012; Ang et al. 2018; Frenzel et al. 2018). Thermophiles have repeatedly been proposed as sources of industrially relevant thermostable enzymes (Schuerg et al. 2017). For example, the hyperthermophilic bacterium *Thermotoga maritima* MSB8 produces nitrilase (optimum temp. 45 °C and pH 7.5). The nitrilase gene consists of 804 nucleotides encoding a protein of 268 amino acidic residues with a molecular mass of 30.07 kilodaltons (kDa) after sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis (PAGE) analysis. The nitrilase has been found to be a potential candidate for industrial applications on the biosynthesis of carboxylic acids (Chen et al. 2015). On other hand, novel eukaryotic thermostable DNA polymerases (dPol) have been developed for the rapid detection of *Mycoplasma*, *Ureaplasma* other bacteria and pathogenic fungi in amniotic fluid (Ueno et al. 2015; Venev and Zeldovich 2017).

Table 2. Industrial applications of thermostable enzymes in biotechnological processes

Thermostable enzymes/ Product	Species	Industrial applications	Reference
Acid Proteases	<i>Brevibacillus</i> spp. OA30	Production of bioactive peptides from casein	Guinane et al. 2015; Gomri et al. 2018
Alkaline Proteases	<i>Bacillus subtilis</i> Y-108, <i>Bacillus licheniformis</i> , <i>Brevibacillus</i> spp.	Detergent industries	Ramkumar et al. 2018; Barzkar et al. 2018
Amyloglucosidase, Glycosyltransferase, Glycoside hydrolase and Transglycosylase, Pullulanase, β -Glucanases	<i>Thermus thermophilus</i> , <i>Thermus scotoductos</i> , <i>Bacillus stearothermophilus</i> , Alkalophilic <i>Bacillus</i> sp.I-5, <i>Rhodothermus obamensis</i> , <i>Neisseria polysaccharea</i> , <i>Deinococcus geothermalis</i> , <i>Bacillus stearothermophilus</i> , <i>Thermus</i> spp.,	Food and baking industry	Singh et al. 2016; Do et al. 2016; Baroroh et al. 2017; Park et al. 2018
α -Amylase	<i>Bacillus licheniformis</i>	Industrial applications in unconventional and economical substrate viz. waste management problem of agro-industrial	Rekadwad and Pathak 2016; Awan et al. 2018

		waste of potato peels	
β -Amylase	<i>Bacillus</i> spp., <i>Apergillus</i> spp.	Starch degrading sector, food processing factories	Banerjee and Ray 2017
Cellulases, Endoglucanases, β -glucosidase, cellodextrinases	<i>Bacillus amyloliquefaciens</i> , <i>Aspergillus nidulans</i> , <i>Cellulosimicrobium funkei</i> , <i>Xylanimicrobium pachnodae</i> , <i>Humicola grisea</i> var. <i>thermoidea</i>	Biostoning, To release aromatic compounds from fruit and fermentation, Juice clarification, Pharmaceutical industry	Escuder-Rodríguez et al. 2018
Hemicellulases	<i>Aspergillus fumigatus</i> JCM 10253	Biofuel industries	Saroj et al. 2018
Inulinase	<i>Kluyveromyces marxianus</i> , <i>Cryptococcus aureus</i> G7a, <i>Bacillus smithii</i> T7, <i>Aspergillus awamori</i> , <i>Arthrobacter</i> sp. S37, <i>Streptomyces rochei</i> E87, <i>Xanthomonas</i> spp.	Biorefining, higher value-added production	Qui et al. 2017 ; Bhagia et al. 2017 ; Khatun et al. 2017 ; Qiu et al. 2017
Invertase or β -D-fructofuranosidase fructohydrolase	<i>Bacillus cereus</i> , <i>Bifidobacterium adolescentis</i> G1, <i>Lactobacillus reuteri</i> CRL, <i>Thermotoga neapolitana</i> DSM 4359T, <i>Arthrobacter globiformis</i> IFO 3062, <i>Lactobacillus brevis</i> Mm-6, <i>Zymomonas mobilis</i> CDBB-B603	Functional food with prebiotic ingredients	Lincoln and More 2017
Lactase	<i>Aspergillus oryzae</i> , <i>Aspergillus niger</i> , <i>Aspergillus sphaericus</i> , <i>Kluyveromyces</i> , <i>Streptococcus</i> spp.	Food Industry	Grace et al. 2017
Lipases	<i>Thermoanaerobacter thermohydrosulfuricus</i> (LipTth) and <i>Caldanaerobacter subterraneus</i> subsp. <i>tengcongensis</i> (LipCst)	Highly S-stereoselective toward esters of secondary alcohols. Kinetic resolution of synthetically useful compounds.	Royter et al. 2009 ; Widowati et al. 2017 ; Rigoldi et al. 2018
Neutral Proteases	<i>Aspergillus oryzae</i> Y1	Pea sauce production in the food processing industry	Ao et al. 2018
Pectinases/ Polygalactouronase	<i>Aspergillus niger</i> , <i>Chryseobacterium indologenes</i> strain SD, <i>Citrus nobilis</i> var. <i>chrysocarpa</i>	Fruit processing, Fruit juice clarification	Sandri and da Silveira, 2018 ; Roy et al. 2018
S-Layers proteins	<i>S. acidocaldarius</i> , <i>S. marinus</i>	Gold (Au) nanoparticle production, As a drug delivery system	Rodrigues-Oliveira et al. 2017 ; Pohlschroder et al. 2018 ; Khursigara et al. 2018
Taq DNA Polymerase	<i>Thermus aquaticus</i> YT-1, <i>Thermus brockianus</i> GE-1,	Possesses a 5'→3' polymerase activity and a 5' flap endonuclease	Kreff et al. 2017 ; Sundarrajan et al. 2018

		activity. Primarily used in DNA fragment extension reactions popularly known as polymerase chain reaction (PCR)	
Thiol proteases	<i>Bacillus subtilis</i> AKAL7, <i>Exiguobacterium indicum</i> AKAL11	In leather industry for de-hairing of skin	Hakim et al. 2018

Biorefineries for production of commodity chemicals using renewable resource

The development of microbial products in biorefineries and their use for the sustainable biotechnology is also influenced by ethical, political and economical concerns (Boldrin et al. 2013; Glaser et al. 2018; Puentes-Téllez and Salles 2018). Overcoming exceptions to these drawbacks, in near future, thermostable enzymes and thermophiles are highly relevant for the required advancements demanded by modern biotechnological industry for the benefits of mankind and society especially in developing countries.

The use of enzymes, or natural biocatalysts, transformations of purely chemical processes into biochemical processes in a sustainable way is the aim of White Biotechnology. Thermostable enzymes used in various bioprocesses (Zarafeta et al. 2016a,b,c; Quehenberger et al. 2017; Liang et al. 2018) and biorefineries are important start-ups and currently highlighted ways to produce renewable raw materials, industrially important intermediates and final products having low volume with high value and vice versa (Fig.3) in the “White Biotechnology” revolution. Broadly, thermophiles are potential major players in modern biotechnology. Expansion of the unimaginable power of enzymes, and specifically those from thermophiles, to synthesize products that are stable, useful, effortlessly degradable with utilization of minimal energy and generation of wastes (Frazzetto 2003; Fernandez-Cabezon et al. 2018) using recyclable and sustainable raw materials (i.e., biomass). Through the use of biorefineries, at present, it is possible to convert feedstocks into commercially useful biological products (Ferraz Júnior et al. 2016; Guo et al. 2017; Huang et al. 2017; Chandel et al. 2018; David et al. 2018). Therefore, metabolically active thermophiles are very important for biocatalytic conversions of raw materials in utilizable forms for the generation of metabolizable building blocks (such as sugars from polymers) and desired products through oxidations, reductions, hydrolysis, carbon-carbon bond formations and enzyme catalysis. For instance, hydroxylation Baeyer-Villiger oxidation reactions carried out by monooxygenases (Kadowaki et al. 2018), alcohol dehydrogenases produced by thermophiles through stereoselective reduction of carbonyl compounds to chiral alcohols (Vitale et al. 2018), toxic chemicals could be replaced by lipases or oxido-reductases through epoxide synthesis (Jia et al. 2017), lyases can form C-C bonds, thermostable transferases and glycoside hydrolases catalyze glycoside synthesis through reverse hydrolysis and produce products such as glyco-oligosaccharides, glycol-conjugate alkyl-glycosides (Rockova et al. 2012; Schröder et al. 2017; Watanabe et al. 2018; Diwan et al. 2018; Dreger et al. 2018) . The use of immobilized whole cells and enzymes in biorefineries increases production of useful building blocks/materials and metabolic products (Akita et al. 2018). Thermostable enzymes must reach high production levels at low cost and high efficiency to achieve highly competitive bioprocesses.

Fig. 3 Overview of biorefineries: Multidisciplinary involvement and potential applications for thermophiles

Second generation ethanol production

A typical example of the use of biomass in biotechnology is the production of bioethanol and, in general, biofuels. Bioethanol production has been significantly improved with the establishment of the second generation processes which enhanced sugar utilization using genetically engineered yeasts. Nevertheless, common pre-treatments of plant residues and biomass include high temperature incubations which suggests the need for thermophiles and their highly thermostable enzymes. Thermophiles are used for the production of biofuel (bioethanol) i.e. non-native alcohols. Bioethanols are produced from complex lignocellulosic biomass due to their higher operating temperatures and broad substrate range which facilitates mixing, substrate accessibility and degradability. High temperature is a critical factor dealt with processing highly viscous syrups obtained from vegetal biomass which can be used as raw material in later steps (Strang et al. 2017). Later steps of ethanol production can be carried out using aerobic bacteria and yeasts and anaerobic bacteria. Herein we have the focus on the main orders of anaerobic thermophiles, for example, Thermoanaerobacterales known to produce ethanol (Zheng et al. 2018). Physiology and relevance of various environmental factors, including the partial pressure of hydrogen, ethanol tolerance, pH and substrate inhibition, allows full growth of Thermoanaerobacterales under anaerobic conditions lead to increased ethanol yields (Scully et al. 2015; Zheng et al. 2018). Moreover, evolutionary adaptation and recent development in genetic engineering of Thermoanaerobacterales would be helpful in batch or simultaneous saccharification, fermentation and consolidated bio-processing (Jia et al. 2017; Basit et al. 2018a, b; Sitthikitpanya et al. 2018).

Thermostable biomolecules and their potential applications

Lignocellulose degrading extremozymes

Lignocellulosic biomass is important to manufacture renewable and biodegradable byproducts (Botha et al. 2018). Extremophilic lignocellulosic enzymes especially beta-mannanases, xylanases, laccases and cellulases, including endo-glucanases, exo-glucanases and beta-glucosidases have potential applications in biotechnology in near future (Ergun and Calik 2016). Many of these enzymes were genetically engineered into *Pichia pastoris*. These genetically engineered extremozymes are superior enzymes with improved stability due to proper post-translational modifications leading to better protein folding. This change in production apparatus shows that the host (*Pichia pastoris*) is highly favored system for production of extremozymes (Gidijala et al. 2018).

Exceptionally, biological process of glycosylation contributes to the structure, stability and function of enzymes (Tian et al. 2018; Ge et al. 2018) expressed in *P. pastoris* and exhibit better thermostability over other non-glycosylated (Yang and Zhang 2018b). In this particular case, there were few reviews on chemical design to enhance synergistic proficient ensuring lignocellulosic proteins. Later studies performed using computational approach with a focus on enzyme activity shows less dependability, enhanced reactivity and high productivity by enzyme is only due to structural changes in catalysts that may leads to significant process modernization (David et al. 2018; Malla et al. 2018). However, there are limited reports available on enzyme engineering to improve catalytic efficiency and stability of lignocellulosic thermoenzymes. Therefore, data generated from metagenomics analysis would be utilized for exploitation and discovery novel enzymes (Kuancha et al. 2017). Thus, in near future, studies should have focus on protein engineering based on stable natural models, mainly from thermophilic microorganisms, to improve stability and catalytic efficiency using modern approaches. Taxonomists, molecular microbiologists and genetic engineers should continue search and have thrust to find new metabolic pathways, natural processes in existing microorganisms using metagenomics, metatranscriptomics (Rekadwad and Ghosh 2018; Rekadwad, 2018a,b,c), computational modeling, mutations, domain replacements and fusion enzyme technology (Lee et al. 2018) approach to perform specific processes for the goal to be achieved.

Another study of biomass degradation is the examples of a cellulase and two esterases from environmental *Geobacillus* strains obtained from metagenomic sequence data. These enzymes degrade lignocellulosic materials, optimally between 40°C and 70°C, and, interestingly, they showed an increase in activity when supplemented with barium (BaCl₂) (Muñoz et al. 2016).

Thermostable esterases

Thermostable esterase (Estgela) produced by a moderate thermophile *Bacillus gelatini* strain KACC 12197KA (Kim et al. 2015). Esterases encoding genes were also found in the *Thermus filiformis* (Mandelli et al. 2017). Estgela enzyme (a novel thermostable esterase from *Bacillus gelatini* KACC 12197 (Kim et al. 2015) (molar mass 42 kDA) contains 389 amino acids. The BLASTx results of Estgela shows similarity with β -lactamases and esterases (43%). The cloned SerXXLys conserved sequence (Ser58Met59Thr60Lys61) of Estgela gene in *Escherichia coli* XL1blue showed a remarkable enzymatic activity toward *p*-nitrophenyl-ester with short four carbon acyl-chains and the strongest activity towards *p*-nitrophenyl-butyrate (Kim et al., 2015a). Estgela shows maximum activity at 65-75 °C and 180 min after incubation at 65 °C retained more than 90% of the initial activity. Furthermore, Estgela showed the maximal activity at pH 10. Surfactants were effectively improved the

enzymatic activity of Estgela (Antonopoulou et al. 2018). Estgela was capable to hydrolyze (both *R* and *S*) ketoprofen-ethyl-ester with enantio-selectivity toward (*S*)-ketoprofen-ethyl-ester rather than (*R*)-ketoprofen-ethyl-ester which represents a significant improvement because of the role of these compounds in the degradation of biomass and industrial pollutants (Mäkelä et al. 2018; Romero et al. 2018). Moreover, esterases are also useful in the synthesis of optically pure compounds, perfume, and antioxidants (Mandelli et al. 2017; Botha et al. 2018).

Potential applications of keratinases

Keratin is cosmopolitan in natural fibre. Animal body parts such as hair, nails, hoofs, feathers and horns are recalcitrant structural proteins with high number of disulfide bridges (Middelveen et al. 2018; Navone and Speight 2018). Keratinases are proteolytic enzymes that attack disulfide bridges of keratin. Therefore, keratinases are useful in preparation of animal nutrients, textile processing, leather manufacture, detergent formulation, protein supplements, the pharmaceutical and biomedical industries, feather meal processing for feed and as fertilizers, and waste management (Barman et al. 2017; Banerjee and Ray 2017; Verma et al. 2017; Hakim et al. 2018).

Generally, keratinases are produced in batch culture (Drejer et al. 2018). It is necessary to produce keratinase from economic raw sources using microorganisms (Reddy et al. 2017). Saloons, abattoir and mundan (donating hair) at sacred places are best sources for raw keratin. This bulk keratin could be exploited for the production of microbial keratinases obtained from Fungi, Bacteria, and primarily Actinomycetes. These microbial keratinases are less expensive than conventionally produced keratinases.

Keratinolytic thermophilic fungi

Few reports are available in recent days on keratinolytic thermophilic fungi. Keratinolytic thermophilic fungi are capable of producing keratinases from keratin-containing waste materials (Kanoksilapatham and Intagun 2017; Zhang et al. 2018). Applications of keratin degrading thermophilic fungi could be deduced based on studies on moderately thermophilic or mesophilic keratinolytic fungi showing their potential. A number of keratinolytic fungi utilize native keratin as a sole carbon (C) and nitrogen (N) source for their growth and multiplication. The keratinophilic fungi of group Hyphomycetes include both dermatophytic (e.g., *Microsporum*, *Epidermophyton*, and *Trichophyton*) and nondermatophytic (e.g., *Chrysosporium* and other genera) keratinophilic fungi (Suaria et al. 2018). Keratinolytic thermophilic fungi were abundant in soils nearer to Earth's equator and up to tropics. They shows high abundance in waste keratin samples in some areas such as public gardens (65%), waste from schools and saloons (52%), poultry farms (43%), garbage (34%), hospitals (30%) and rivers (21%). It is reported that keratinophilic fungi are dominant in areas inhabited by humans and animals (Saggu and Mishra 2017).

Keratinophilic Fungi produce sulfide through sulphitolysis and, during this process, the disulfide bonds of cysteine, a major amino acid in keratinous materials, are broken down, after which the proteolytic enzymes released by the fungi that can easily cleave the keratin. During the degradation process, the products released are cysteine, S-sulphocysteine and inorganic sulfate, and the presence of these products in the culture media indicates the occurrence of true keratinophilic Fungi (Zhang et al. 2018). For wide applicability of keratinophilic fungi in biotechnology, modification in disulfide bridges and addition of covalent bonds would be an appropriate solution for improvement in thermostability of keratinophilic fungi.

Keratin-degrading bacteria

Thermophilic bacteria have advantages over fungi because of fast growth rate and inherent characteristic possessed by them. Among the keratinase producing thermophilic bacteria some belonging to Gram positive bacteria include *Bacillus subtilis*, *B. licheniformis*, (Abdel-Fattah et al. 2018; Singh et al. 2018; Dreger et al. 2018), *Burkholderia* (Huang et al. 2018), *Lysobacter* (Laba et al. 2018), *Nesterenkonia*, *Kocuria*, and *Microbacterium* (Nouioui al. 2018) and Gram-negative bacteria include *Chryseobacterium* (Navone et al. 2018), *Fervidobacterium*, *Stenotrophomonas* (Wang et al. 2017), *Thermoanaerobacter*, *Xanthomonas*, *Nesterenkonia* and *Vibrio* (Laba et al. 2018). Moreover, Actinomycetes, *Streptomyces* group, namely, *S. fradiae*, *Streptomyces* species A11, *S. pactum*, *S. albidoflavus*, *S. thermoviolaceus* SD8, and *S. graminofaciens*, as well as *thermoactinomyces candidus*, were capable of producing keratinase (Nouioui et al. 2018).

An example to search for keratinases from hyperthermophilic bacteria is the genus *Fervidobacterium* (Thermotogae). Some species of this genus are capable of completely degrade feathers in cultures, suggesting highly keratinase activity within this genus (Kanoksilapatham et al. 2016).

Thermophilic dihydroxyacetone phosphate (DHAP)-dependent aldolases

The potential of aldolases contributes to the development of greener and sustainable processes because they contribute to the decomposition of sugars both actually breaking down the sugar molecule into smaller components, as well as activating subsequent metabolic pathways which can potentially enhance biotechnological processes. Four different kinds of structurally characterized DHAP-dependent aldolases were described up to now. Only few aldolases have been studied for stereo-selectivity although they may not be commercially available yet. Thermostable aldolases may contribute and eliminate current limitations of aldolases viz. poor product yields or short half-life span encountered with previous DHAP-dependent aldolases. Of these Fructose 1, 6-bisphosphate (FBP) aldolase (FBPA, EC 4.1.2.13) from (hyper)thermophilic have been intensively studied because of their physiological role(s) in glycolysis and gluconeogenesis (Falcicchio et al. 2014). The active system of biozyme Mja-FucA may advance the development of a robust model for carbon-carbon (C-C) coupling at extremely high temperature to test (hyper)thermostable biozyme in sensitive field of hilter kilter combination (i.e. asymmetric synthesis). To avert dihydroxyacetone phosphate (DHAP) in system involving water, synthesis in natural polar and nonpolar organic solvents might be an answer (Puckett et al. 2014; Hartley et al. 2017; Visone et al. 2017; Mohammad et al. 2017; Yokoyama et al. 2018). In any case, this method has been so far ineffectively explored in both mesophilic and thermophilic proteins, because DHAP are pernicious for biochemicals. (Hyper)thermophiles could have an ability to enhance the productivity under hardish conditions and at uplifted temperatures (Falcicchio et al. 2014). Downstream process of these products at high temperature may help to improve amalgamation and partition of product(s). On other hand, imperative catalysts from (hyper)thermophiles that would built biocatalytic variants. (Hyper)thermophilic DHAP-subordinate aldolases are less stereoselective than mesophilic ones (Joseph et al. 2018).

Apparently, lack of stereoselectivity aligned with the extreme stability of many (hyper)thermostable enzymes may be a solution to develop versatile and robust biocatalysts stable at high temperatures.

Acetogenesis by thermophilic anaerobes

Anaerobic bacteria produce acetate through Wood-Ljungdahl pathway from carbon dioxide and a source of electron such as hydrogen, carbon monoxide, formate etc. This

process is called acetogenesis. The process of acetogenesis carried out by thermophilic bacteria, is termed 'Hot Acetogenesis'.

Only a few acetogenic bacteria within the thermophiles have been reported. Members of the family *Thermoanaerobacteraceae* such as *Moorella* spp., *Thermoanaerobacter* kivui and *Thermacetogenium phaeum* conserve energy from hot acetogenesis. These organisms possess potential biochemical pathways for energy recovery from greenhouse gas (i.e., CO₂) under anaerobic conditions (Basen and Müller 2017; Ma et al. 2019). This would be a potential alternative energy strategy for conservation energy because acetate is a major intermediate, for instance, during bio-fuel producing processes.

Biodegradation of polycyclic aromatic hydrocarbons (PAHs)

Extremophiles, including thermophiles, also have ability to colonize surfaces and deep subsurfaces in extreme environments such as hydrocarbon polluted sites and petroleum reservoirs (Sierra-Garcia et al. 2017). These reservoirs are rich in PAHs. PAHs are environmental pollutants showing deleterious effects to biodiversity and ecosystem health. Extremophilic microorganisms and specially thermophiles and halophiles possess known established mechanisms for the biodegradation of PAHs through environmentally friendly pathways. The bacterium *Stenotrophomonas maltophilia* strain AJH1, *Bordetella avium*, *Desulfomicrobium* and many other strains are capable of degrading low molecular weight and high molecular weight PAHs. One constraint about PAH degradation is to achieve adequate PAH dissolution. By doing high temperature processes, PAH dissolution is increased and this could represent a great opportunity to use thermophiles to obtain higher PAH degradation efficiencies. Thus, the use of thermophiles and other extremophiles for the treatment of hydrocarbon polluted industrial waters and oil spills would be a novel and environmentally friendly technology (Arulazhagan et al. 2017; Wolfson et al. 2018; Abo-State et al. 2018; Marozava et al. 2018).

Biotechnological applications of mobile group II introns (MGIs)/Targetrons (TTNs)

Versatile MGIs are bacterial retrotransposons. They have capacity to recognize base pairing in DNA target sites, catalyze the reaction, achieve high DNA target specificity and couple correct base pairing (Mohr et al. 2010; Mohr et al. 2013). These targetrons have vast application viz. enable gene targeting and genetic engineering of bacteria. A thermostable targetron has been developed for use in thermophilic bacteria (Rekadwad et al. 2017; Baronti et al. 2018). Position for recombinase recognition sites enable large-scale genome-editing operations, such as insertions, deletions, inversions and translocation of large DNA segments can be developed using targetrons (Enyeart et al. 2014; Bou-Nader et al. 2018). MGI reverse transcriptases can yield large amounts of highly active proteins. These bacterial thermostable MGI reverse transcriptases are being used as research tools for a variety of applications such as qRT-PCR, new generation RNA sequencing, etc.

Improvement in thermostability through mutation/s

Enhancement of thermostability of moderate thermostable enzymes could be achieved through modification in enzyme structure (Vanz et al. 2012; Attri et al. 2018), specific covalent bond modification (Darby et al. 2017). For example, introduction of disulfide bridges and elimination of native biochemical bonds, generally, help to expand thermostability of enzyme. Esterases such as A-feruloyl-esterase (AuFaeA) produced by *Aspergillus usamii* (A. usamii) E001 were thoroughly studied for improvement of thermostability and applications in biotechnology. DSDBASE (<http://caps.ncbs.res.in/dsdbase/dsdbase.html>), MODIP (<http://caps.ncbs.res.in/iws/modip.html>) and DbD2 (<http://cptweb.cpt.wayne.edu/DbD2/>) (Yin

et al. 2015a; Song et al. 2018) are the three computational tools that could give an idea about anticipated disulfide bridges in enzymes/or proteins. These databases can allow us to check possible improvement in thermostability of enzymes or proteins (Pezeshgi et al. 2018). Similarly, molecular dynamics (MD) simulations (e.g. AMBER, CP2K, CPMD, Gromacs, etc.,) were used to design potential disulfide bridges to be incorporated into proteins. Modifications such as increasing of disulfide bridges in proteins can be carried out by mutations one residue pair A126-N152 to cysteine and expressed in *Pichia pastoris* GS115 (Liu et al. 2016; Zhou et al. 2017). Moreover, incorporation of the local disulfide bridges in AuFaeA results in a great decrease in expression level by 10°C (Uraji et al. 2014; Yin et al. 2015b; Alvarez et al. 2016; Broeker et al. 2018). Therefore, improved and modified thermostable AuFaeA like variant may find applications in the enzymatic degradation of plant biomass materials at elevated temperatures.

Conclusion

Thermophiles and thermozymes are necessary due to their high activity and stability at high temperatures. They can reduce the cost of production of biomolecules from low-cost raw biomaterials. The cost-effective translation of substrate into useful products for commercial applications using prokaryotes and eukaryotes (i.e., biotransformations) steadily contributes and replaces traditional catalysts in chemical process. Thus, biotechnologically and commercially important high-value and low-volume and low value-high volume byproducts generated using thermophiles are useful in healthcare, medicine, agriculture and pharmaceuticals.

Future perspectives

This review discussed some examples of novel initiatives enhancing the potential of White biotechnology involving the use of thermophiles and thermozymes. New biomolecules and thermophiles are waiting to be discovered for their innovative application and an unimaginable power of genes for improving and strengthen biotechnological processes, some of which remain to be commercially applied. There is a need to design new procedures and protocols for the cultivation of novel thermophiles having applications in biotechnology, agriculture, medicine and healthcare. In addition, culture-independent techniques remain as a major source to retrieve novel enzyme-encoding genes of high biotechnological potential. In summary, the potential for applications of biocatalytic durables-thermostable enzymes-with expanded specificity and high efficiency has been shown for numerous thermophiles and thermozymes but their commercialization should be accelerated for society to profit today from current knowledge.

Conflict of Interest

All authors declare that they have no conflict of interest.

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