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Emerging priorities for microbial metagenome research

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ABSTRACT

Overwhelming anthropogenic activities lead to deterioration of natural resources and the environment. The microorganisms are considered desirable, due to their suitability for easy genetic manipulation and handling. With the aid of modern biotechnological techniques, the culturable microorganisms have been widely exploited for the benefit of mankind. Metagenomics, a powerful tool to access the abundant biodiversity of the environmental samples including the unculturable microbes, to determine microbial diversity and population structure, their ecological roles and expose novel genes of interest. This review focuses on the microbial adaptations to the adverse environmental conditions, metagenomic techniques employed towards microbial biotechnology. Metagenomic approach helps to understand microbial ecology and to identify useful microbial derivatives like antibiotics, toxins, and enzymes with diverse and enhanced function. It also summarizes the application of metagenomics in clinical diagnosis, improving microbial ecology, therapeutics, xenobiotic degradation and impact on agricultural crops.

1. Introduction

The biosphere is comprised of living and non-living components that are interlinked in a complex manner to form a propitious environment. Unreceptive changes in the biotic or abiotic components of the environment lead to disastrous changes at every level of the ecosystem. For example, the scarcity of water directly affect the agricultural output which not only affect the humans, the direct consumers, but also various insects, birds and animals and even the soil microbes which depend on the plants for the nutrition (Han et al., 2007). The anthropogenic activities lead to major devastations of the environmental components viz. changes in biogeochemical cycles, pollution and loss of biodiversity. Owing to the increasing population, over exploitation of the natural resources, urbanization and industrialization contribute their part to the environmental changes (Otto et al., 2020; Couce et al., 2020). Considering the antiparallel concerns of ever-growing need for natural resources and food products versus the drastic environmental changes and deterioration of sustainable resources, there always exists a drive to address these challenges, through novel technological interventions. To search for a novel sources or products is a never-ending journey where, various technologies, organisms and their products were explored to attain the growing needs.

The advancement of biotechnological tools, resulted in genetically modified organisms (microbes, plants and animals) to meet the nutrition- oriented needs (Rodriguez et al., 2006; Ghaga and Ganapathi, 2017; Forabosco et al., 2013; Fahrenkrug et al., 2010), whereas various physical, chemical and biological technologies were successfully employed for environmental management (Gomes et al., 2016; Rajakaruna and Robinson, 2016; Lim et al., 2014). Microorganisms are convenient for genetic manipulations and other logistical requirements; therefore many of these needs and issues were addressed through them in effective and eco-friendly manner (Dixon et al., 2020). It is worth noting that, there are numerous beneficial bacteria existing in the environment but is not suitable for laboratory culture or genetic manipulation that can be explored using the metagenomic tools. Taken together, the increasing needs for food, medicinal and industrial products and imminent global issues like loss of natural habitats and biodiversity, heavy metal and xenobiotic pollution, disturbance of terrestrial and aquatic ecosystem demand an effective solution to achieve sustainable food resources and environment management.

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This review highlights various roles and adaptations by the microbes in the environment and thus summarizes the significance of metagenomics and its sub-disciplines. This review also describes the current methods and stratagems used in metagenomics with respect to different environmental sources of the beneficial un-culturable microorganisms with the prominence to sequence-driven and function-driven analysis of metagenome. In addition to the environmental and agricultural benefits, the application aspects of metagenomics in the food, enzyme, pharmaceutical industries and clinical settings are discussed. The usefulness of metagenomic approach with respect to environmental management through bioremediation and balanced microbial ecology are elaborated in the following sections.

1.1. Beneficial adaptations by the microbes

Microorganisms boom all the way through natural world, and microbes have adjusted to endure under a wide range of punitive or unaccommodating conditions, ensuing in adaptation by the microorganisms to specific niches (Edge et al., 2020; Handelsman et al., 1998). These adaptations by the microbes lead to evolution of meritorious phenotypes, which could be further exploited for prospective biotechnological applications (Grossart et al., 2020; Hamner et al., 2019). For example, following the success of *Taq DNA polymerase* from *Thermus aquaticus*, a thermophile, and similar trends followed isolate important enzymes like pfu from *Pyrococcus furiosus* (Singh et al., 2019). Two lipases belonging patatin-like phospholipase family from hot springs and a naphthalene catabolic gene from oil contaminated sites were isolated through metagenome approach (Awasthi et al., 2020; Yooseph et al., 2013). Moreover, current estimations show that 99% of the microbes existing in many natural environments are not readily culturable and therefore not available for basic or biotechnology research (Boifot et al., 2020). This assessment suggested that an alternate microbial biotechnological technique could provide an insight into these particularly modified exclusive microbes, their potentially useful gens or genome outlines (Kirubakaran et al., 2019).

1.2. Metagenomics – an alternative tool

Metagenomics, a powerful technique involves isolation of genomic DNA directly from the environment, without the need for prior culturing of organisms under laboratory conditions (Singh et al., 2019; Wang et al., 2000b). Analysis of the total metagenomic DNA by sequencing can reveal information about numerous features of the sample, which enables us to thoroughly understand the microbiome in any given environment i.e. air, water and soil (Meneghine et al., 2017; Behzad et al., 2015; Gastauer et al., 2019). Metagenomics involve pyrosequencing technology, as one of the alternatives to the usual dideoxynucleotide-sanger method for metagenomic DNA sequencing that provides reliable data about the important genes involved in the decontamination of environmental pollutant residues (Ibekwe et al., 2013). Mining of genetic information directly from environmental samples can also overcome in part, the barriers faced by the cultured bacteria (Steele and Streit, 2005). Although functional metagenomics, a powerful technique for the discovery of novel functional genes from unculturable microorganism which involves screening of the subsequent phenotypes by the artificially transforming metagenomic DNA in a suitable host to uncover a desired activity/product (Lim et al., 2014; Otto et al., 2020). The existence of so many novel gene families from these rich microbial diversity and uncultured populations pose a challenge for the understanding and exploration of the environmental microorganisms (Gilbert and Dupont, 2011; Schallmey et al., 2011). Based on literature evidences, the microbial population will undoubtedly undergo a further symbiotic shift or conjugation (vertical or horizontal) which will lead to recombination and evolution of novel strains with greater significance (Tilwari et al., 2013; Kirubakaran et al., 2017). Under these circumstances, metagenomics disciplines such as meta-transcriptomics, meta-proteomics, metabolomics and functional enzyme discovery can be successfully employed to extract the systematic information of the samples (Cheema et al., 2012; Hess et al., 2011). Recently, metagenomics has been nurtured by the recreation of natural environmental settings combined with focused screening for novel discovery of industrial enzymes and drugs (Sarsaiya et al., 2019; Yao et al., 2011). Therefore, both primary and applied approaches have contributed to the discovery of novel products (Wilson, 2009). Hence, it is crucial that both natural environmental science and effective screening to be pursued as part of the innovative field of metagenomics (Shakoor et al., 2019).

2. Metagenomic approach towards microbial biotechnology

The sample collection and the downstream techniques are crucial in terms of quality and quantity to achieve a rich metagenomic library. The sampling procedure might have few limitations or challenges, which need to be addressed carefully to achieve a successful metagenome library. The sample collection and processing for metagenomics vary slightly based on the type of environment (i.e. air, water and soil). While sampling the air, it should be noted that the sampler collects the solid particles, cells of different origin including human, insects, pollens and protozoans, which require intensive filtration before extracting the DNA (Sabale et al., 2019; Samarkos et al., 2018). Soil samples form a different complication, where different layers of the soil habitat different group of microbial community, hence it is crucial to select the appropriate layer of the soil for the analysis (Putra et al., 2019; Ngara and Zhang, 2018). The water samples diverge widely ranging from pure drinking water with minimal particulates to heavily polluted water, which is rich in minerals, microflora and fauna, which need exclusive filtration procedures (Nelkner et al., 2019; Nakagawa and Fujita, 2018). The following sections will discuss the significance of metagenomics in various environments and individual sampling and post-process methods for the metagenomic DNA isolation from air, soil and water samples in detail.

2.1. Metagenomic approach towards air

Microorganisms are far and wide in the air and is estimated that the concentrations approximately range between 10^4 and 10^6 microbes/m^3. Previous studies suggested that microbes in atmospheric air are metabolically active, for example, in biogeochemical cycles they play prominent roles and act as a catalyst in natural processes such as nucleation of ice and cloud formation (Conrad et al., 2016; Nelkner et al., 2019). It is worth noting that the increased cloud formation may possibly be implicated for earth global warming and climate changes; despite these crucial contributions, there are fewer reports on the probable impact of atmospheric microorganisms upon the environment (Gilbert and Dupont, 2011). Metagenomics has provided the information about atmospheric microbial diversity and their crucial metabolic impact on climate changes by molecular analysis of microbial genome through culture-independent studies (Schloss and Handelsman, 2003; Lorenz et al., 2002). For metagenomic analysis, the air samples are collected using dry filter air sampler which are usually operated at a flowrate of 450 L/min and the samples are collected into the sterile sampling buffer for a required amount of time (varies between 2 and 12 h) depending on the environment. The sampling buffers are stored at 4 °C until further use and maintained under aseptic condition throughout the procedure. The samples were further fractionated through different filters of size 3.0 μm to 0.1 μm to remove any unwanted biological substances other than the desired metagenomic DNA. BSL-II hoods and reagents sterilized with UV light are used to extract DNA with the available commercial kits. Interestingly, few reports suggest that, due to the low density of microbes in the air, the DNA isolation must be coupled with an amplification of DNA fragments step to facilitate adequate recovery of the DNA (Fig. 1A) (King et al., 2016;

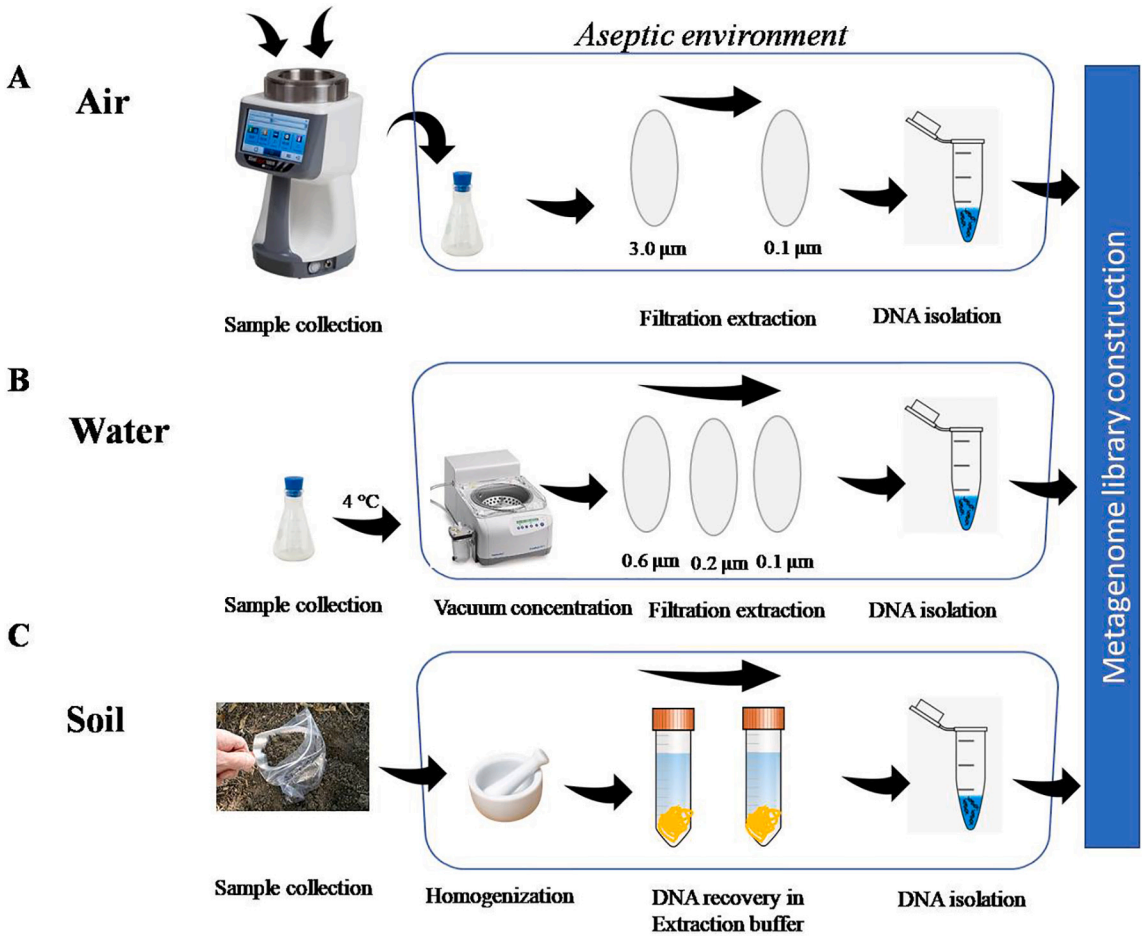

Fig. 1. Schematic representation of sample collection, processing and metagenomic DNA extraction from air (A), water (B) and soil (C).

Behzad et al., 2015; Yooseph et al., 2013; Ung et al., 2020).

2.2. Metagenomic approach towards water

Microbes are found abundantly in both fresh and marine water bodies and play a prominent role in maintaining ecosystem and water quality. Importantly, they play a crucial role in maintaining biogeochemical cycles and dissolved chemical constitution in water ecosystems (Shakoor et al., 2019; Sabale et al., 2019). The usability of water bodies is mainly determined by the dissolved oxygen, electrical conductivity, oxidation reduction potential, hydrogen ion concentrations, dissolved solids and turbidity (Mendes et al., 2014; Pan et al., 2014; Mason et al., 2014). The chemical composition such as nitrate, ammonia, nitrite, phosphorus and dissolved reactive phosphorus are determined by the titre values of precipitation. The irrigation water with heavy metal pollution, concentrated nutrients, toxins or pathogens can adversely impact the agricultural lands and the food production (Maurice et al., 2013; Gaytán et al., 2020). Therefore, it is essential to monitor the microbial population which directly or indirectly influences the water quality. Metagenomic tools have been in use to assess the microbial population and diversity of water ecosystems. Indeed, it has been used to determine the issues related to anthropogenic impacts on surface waters involving microbial community structure and the resulting re-structural biomes (Lefterova et al., 2015; Boulange et al., 2016; Nakagawa and Fujita, 2018; Samarkos et al., 2018). Microbes also aid with the deprivation and decontamination of toxic pollutants from industrial wastewater, an exogenous or microbial enzyme can be supplied to enhance the system to improve remediation process (Hess et al., 2011; Schloss and Handelsman, 2003; Cheema et al., 2012). Also, to determine the beneficial and pathogenic microbes, metagenomics can be employed as an efficient tool. Through this approach, we can improve the water quality which serves as an important measure to address the issues related to public health (Meneghine et al., 2017; Ahern et al., 2007). For analysis of metagenome, the water samples are collected, usually in triplicates in sterile containers. The water samples, under sterile conditions, are concentrated using vacuum concentrator and subjected to a series of filtration with membrane filters, for example, 6 µm to 0.1 µm sized filters. The meta-DNA can be isolated from those filter membranes using appropriate kit methods based on the manufacturer's protocol (Fig. 1B) (Calderon et al., 2017; Bharagava et al., 2019; Kori et al., 2019; Hamner et al., 2019).

2.3. Metagenomic approach towards soil

The soil microbial population possibly has the highest level of microbial diversity of any environment. Each gram of soil has been reported to be occupied by approximately 10 billion microorganisms and thousands of different microbial species (Putra et al., 2019; Gastauer et al., 2019). Soil microbial community has been widely exploited for pharmaceutical and agricultural benefits and bioremediation of xenobiotics. Recently developed functional metagenomic tools provide relatively quick and extensive information of the metagenome samples, for example, meta-DNA sequencing provides complete sequence information of the DNA extracted at a moderate cost (Yadav et al., 2019; Ibekwe et al., 2013). Natural adaptations by soil microbes, such as soil nourishment, have been successfully employed in refining soil quality and providing effective and inexpensive ways to recycle agricultural biomass (Delmont et al., 2011). A lot of altered biomass remains such as

edible vegetables, drainage, and animal dung are used for fertilizer. Studies have shown that organic matter with its enriched nutrients increased the bacterial diversity of the soil independent of the changes in climate conditions (Biver and Vandenbol, 2013; Biver et al., 2013; Calderon et al., 2017). Furthermore, the use of chemical-based nitrogen fertilizers, phosphorus fertilizers and animal manure-based compost can also enhance the bacterial diversity. Based on these studies, it is evident that the supplement of manure can influence the microbial diversity which in turn can improve the fertility of the soil. Metagenomic tools can be efficiently employed to determine the microbial diversity under different supplement conditions to attain highest level of nutrition enrichment (Chu et al., 2008; Ellila et al., 2019). In addition, Metagenomic approaches are widely used to discover the composition of microbial community and their bioremediation potential in a contaminated environment which will be discussed in biotechnological application section. For soil metagenome analysis, the samples can be collected from different layers of soil based on the need and objective, and the soil samples must be transferred under ice cold conditions to preserve the samples (Deininger et al., 1988; Knapik et al., 2019). The sterile soil samples must be homogenized before extraction of DNA using appropriate technique (Fig. 1C).

A general workflow of metagenomics, post DNA isolation is presented in Fig. 2. Taken together, the metagenomic DNA collected from various environments viz. aerosols, soil and water samples from different sites represent the microbial communities and provide the essential information on their beneficial traits (Nelkner et al., 2019; Ngara and Zhang, 2018).

3. Applications of metagenomics

In an attempt to address the threatening scenario of need for increased food and resources and loss of sustainable resources, metagenomics plays a major role. The metagenomic data from the extreme or adverse environment provide necessary information to strategize the environmental management and develop beneficial products. Indeed, metagenomics is used in numerous applications, for example (i) to analyze the phylogenetic assortment of environmental microbes and establish their role in the ecosystem (ii) to identify the importance of microbial community in agriculture (iii) to explore the acquired adaptations of the microbes for developing effective bioremediation systems (iv) to identify novel genes to synthesize beneficial products like industrially important enzymes, therapeutic molecules and catalysts (v) to analyze the microbiome in the human body for diagnostic and therapeutic interventions. The following sections will discuss the above-mentioned applications of metagenomics under various domains (Fig. 3).

3.1. Ecological application

Environmental microbes govern the biosphere and majority of them have not been studied completely (Yadav et al., 2019; Gastauer et al., 2019). Microbial consortia permit the scientists to carry out studies on natural communication and co-habitation (Hirsch et al., 2010; National Research Council, 2007). Mutualism, parasitism, competition, predation neutralism, amensalism and commensalism play a major role in the stability and dynamics of microfloral communities; consequently, co-culturing enables the detection of complex interaction networks, as well dependent or independent signalling molecules (Delmont et al., 2011; Kori et al., 2019; Broderick et al., 2010).

Since the invention of microscope, we are able to study only less than 1% of microbes and the rest are not easily accessible for the research because, the standard culturing practice is not helpful to study them (Schloss and Handelsman, 2003; Stanley and Sadowsky, 2015). Metagenomics provides a distinct path to evaluate the microbial community that not only will transform modern tools of bacterial genetics but has the possibilities to reform the understanding of the entire living world and their functions in different ecosystems (Kirk et al., 2004; Wu et al., 2015; Miura et al., 2017; Chodak et al., 2013). In fact, most powerful genomics analysis is applied to the whole community of microbes, bypassing the need to isolate and culture individual bacterial population portion in array to classify the microorganisms in the community (Steele and Streit, 2005; Alvarenga et al., 2017; Palackal et al., 2007). The track of microbial community is important in a habitation as the microorganisms maintain or modify the environment and it is also responsible for survival of surrounding organisms (Garland and Mills, 1991; Joergensen and Wichern, 2008; Docherty et al., 2015). Metagenomics play a momentous role in understanding the microbial population structure and change in an ecological array. Our present trend of knowledge about the media dependent techniques is unable to achieve the complete portion of microbial diversity and functioning of microorganisms residing even in a single environment (Bharagava et al., 2019). Thus, the novel methodology holds the potential to overcome the difficulties to capture the complete profile of microbial diversity (Chodak et al., 2013; Leckie, 2005; Liu et al., 1997; Sklarz

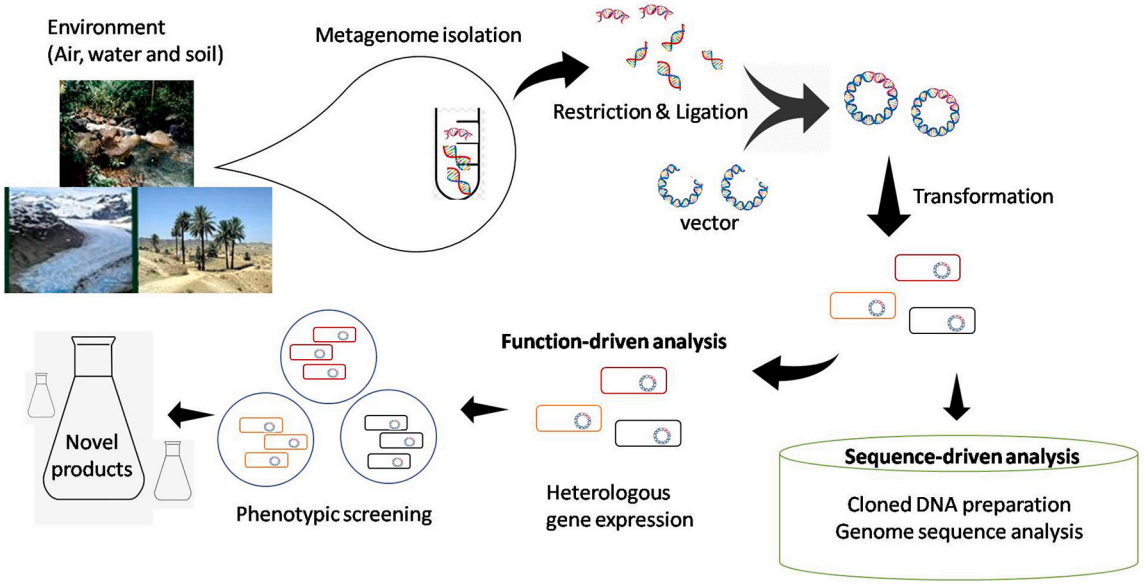

Fig. 2. Schematic representation of metagenomic strategies for the identification of novel products (biocatalysts and bioactive compounds) from environmental DNA.

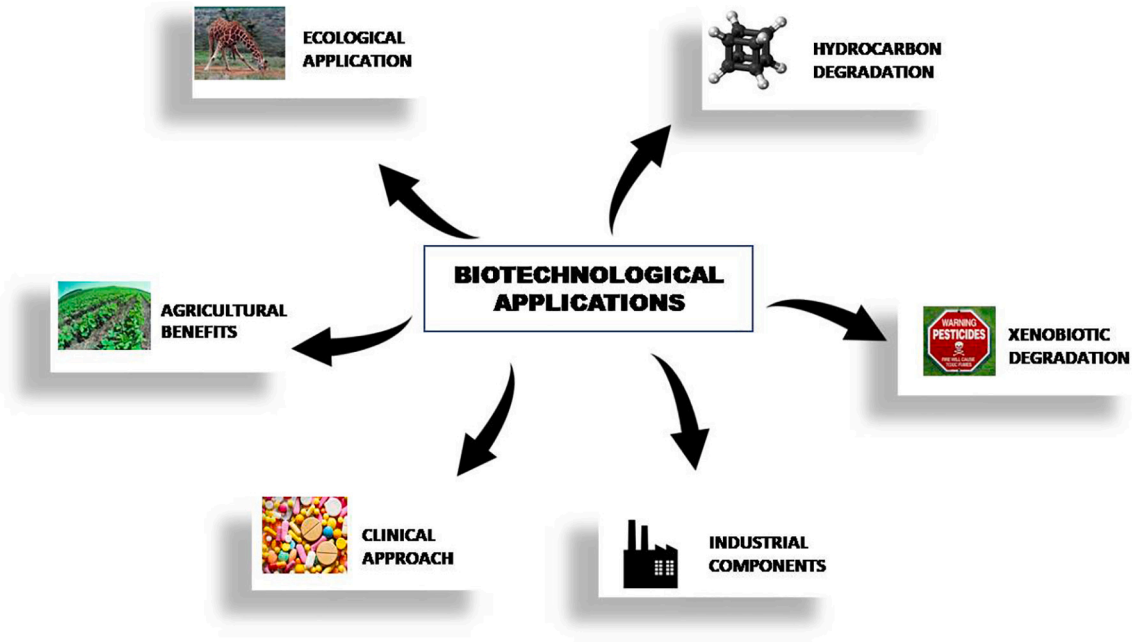

Fig. 3. Application aspects of metagenomics.

et al., 2009). While *in silico* tools considered the biomolecules, microorganisms, and their interaction, as one whole component, metagenomics provide novel directions to experiments and advances in functional tools, such as meta-transcriptomics, meta-proteomics, and metabolomics (Ngara and Zhang, 2018; Calderon et al., 2017; Tilwari et al., 2013; Miura et al., 2017). Therefore, metagenomic approach will be an important tool to understand the complex association and how these inter-relationships appear to benefit all other organisms in the environment.

3.2. Agricultural benefits

The field of metagenomics in agriculture helps to discover the habitat and metabolic potential of soil microbiomes, plant growth promoting microorganisms and new genes for better agro-products (Pii et al., 2016; Lavecchia et al., 2015; Gupta et al., 2018; Nelkner et al., 2019). Complex pattern of interactions including commensalism, mutualism, parasitism etc., occur among the microorganisms in the soil that lead to complex genome rearrangement (Carbonetto et al., 2014). The profusion of gene cluster assigned for transcription results in excess nucleotide transport and metabolism, protein modification, membrane and wall biogenesis and intracellular trafficking and secretion in microbiome of cultivated fertilized soils compared to uncultivated soils (Mendes et al., 2014; Johanna et al., 2019). Moreover, metagenomic approaches can also reveal the taxonomic and functionals aspects of microbiome establishment in rhizosphere, which is an essential element of nourishment to plants. Indeed, a shotgun metagenomics approach revealed that the taxonomic and functional diversities of microbial communities in the rhizosphere of soybean plants are based on the metabolic resemblances of the bacteria. The study also stated that the blending of the microbiome community in the rhizosphere is a niche-based process (Pan et al., 2014; Mendes et al., 2014; Rastogi et al., 2013). The shift in taxonomic composition and functional redundancy of microbial communities in rhizosphere properly explains the changes associated with the fertilization and agricultural management. Understanding of the soil and rhizosphere microbiome through soil metagenomics can be used as a guiding line to innovate new agricultural norms for sustainable environment (Bevivino et al., 2014; Souza et al., 2015).

3.3. Hydrocarbon degradation

Large quantities of contaminants, mainly aromatic and aliphatic hydrocarbons having complex chemical structures released into the environment by industrial activities and accidental spills prevail in the environment for a longer time, resulting in contamination of the ecosystem (Meneghine et al., 2017). The enzymes produced by the microorganisms can mediate the degradation and detoxification of hydrocarbons. The biodegradation by aerobic population has been documented by two pathways, involving either by intradiol or estradiol pathway for removal of aromatic rings of di or trihydroxylated intermediate compounds. The anaerobic class of microbial population degrading hydrocarbons in oil fields converts them into bitumen by targeting low molecular weight components (Thomas et al., 2012). However, anaerobic bacteria able to degrade hydrocarbons found in deep petroleum reservoirs have not been isolated and cultured so far. There are numerous wild type bacteria and few genetically modified bacteria like “super bug” are employed in hydrocarbon bioremediation (Gong et al., 2013).

To combat this scenario, metagenomic approach is an excellent avenue for finding new microbial strains and genes, gene clusters that are capable of degrading hydrocarbon contaminants (Pham et al., 2009; Youssef et al., 2009). The screening method for metagenomic clones are customized using atomized oil assay, oil coated agar plate overlay approach (Płociniczak et al., 2011; Karanth et al., 1999). Interestingly, in a study that constructed a metagenomic library from samples collected in an oil reservoir, comprised genes belonging to different pathways including metabolic pathways involved in the biodegradation of aromatic compounds with novel gene arrangements (Burch et al., 2010; Morikawa et al., 1992). Metagenomic approach is considered advantageous since it applies a special community of microorganisms by providing access to the taxonomic as well as functional gene composition (Mason et al., 2014; Garcia et al., 2014; Langelier et al., 2018).

3.4. Xenobiotic degradation

Xenobiotics are often persistent over long time in the environment resulting from human activities and released in large amounts into common sites. Soil Microorganisms in their living environment can

Table 1
Novel enzymes/products obtained through environmental metagenomics.

Microorganism	Enzymes/products	Source	References
Burkholderia territorii GP3	Lipase and foldase	Soil	Putra et al. (2019)
Trichoderma reesei	Xylanase enzymes	Compost	Ellila et al. (2019)
Acidobacteria	Xylanase enzymes	Hot spring sediment soil/water	Knapik et al. (2019)
Non cultured soil borne constituents	Lipase/esterase/proteases	Soil	Calderon et al. (2017)
Non cultured air borne constituents	Drug resistant enzymes	Air	King et al. (2016)
Clostridium hathewayi	β-Galactosidase (cold active)	Soil	Vester et al. (2014)
Splendidus	Alkaline stable family IV lipase	Marine sediment	Peng et al. (2014)
Fibrisoma limi	UDP glycotransferases	Soil	Rabausch et al. (2013)
Bacillus sp.	Alkaline serine protease	Soil	Biver et al. (2013)
Forest soil-derived metagenomic library	Carboxylic ester hydrolases	Soil	Biver and Vandenbol (2013)
Acidobacteria phylum	Lipase (thermostable)	Soil	Faoro et al. (2012)
Uncultured bacteria	Lipolytic activity	Soil	Nacke et al. (2011)
Bacillus sphaericus	Serine proteases	Dessert soil	Neveu et al. (2011)
Tannase superfamily	Tannase (halotolerant and thermostable)	Soil	Yao et al. (2011)
Planococcus sp and *Bacillus halodurans*	Cold adapted β-galactosidase	Soil	Wang et al. (2010)
Plasmodium and *Borrelia sp*	Cellulase (β-glucosidase)	Soil	Jiang et al. (2009)
Parvibaculum lavamentivorans	Esterases	Sea water	Chu et al. (2008)
Pseudomonas fluorescens	Lipase (cold)	Soil	Elend et al. (2007)
Dechloromonas aromatica	Fibrinolytic metalloprotease	Mud soil	Lee et al. (2007)
Neisseria elongata	Esterases	Soil and water	Elend et al. (2006)
Mesophilic soil microbe	Esterases	Soil	Kim et al. (2006)
Pyrobaculum calidifontis	Esterases (thermostable)	Water	Rhee et al. (2005)
Erwinia herbicola	Ice nucleating protein	Air	Morris et al. (2005)
Erwinia ananas			
Psedomonas flourescens			
Pseudoalteromonas atlantica	β-Agarase	Soil	Voget et al. (2003)
Pyrococcus sp.KOD1	Alpha-amylase	Deep sea	Richardson et al. (2002)
Streptomyces, Moraxella, Acinetobacter and Sulfolobus sp.	Lipolytic enzymes	Soil	Henne et al. (2000)
Pseudomonas syringae	Ice nucleating protein	Air	Deininger et al. (1988)
Xanthomonas compestris	Cell surface protein	Air	Ojanen-Reuhs et al. (1997)
Erwinia herbicola	Ice nucleating protein	Air	Turner et al. (1991)
Pseudomonas fluorescens	Ice nucleating protein	Air	Kozloff et al. (1991)

adapt to the presence of xenobiotics in several different ways: (i) toxic xenobiotic can result in the random mutation, (ii) mutations can also enhance the microbial ability to degrade a xenobiotic, (iii) can acquire novel genes encoding catabolic enzymes through horizontal transfer. It has been reported that, some microbial species can degrade large range of xenobiotics, especially poly-aromatic, halogenated and polyester molecules (Ufarte et al., 2015; Yashir et al., 2014; Jeffries et al., 2018; Ferrer et al., 2005). Elucidating the causal mechanisms for xenobiotic resistance and metabolism in microbes will reveal the host microbial communications, novel enzymes and provide an insight for the unexplained toxicity (Maurice et al., 2013; Itzel Gaytán et al., 2020).

The gut microbiome is another important component of xenobiotic metabolism, the response of gut microbial population to the xenobiotics (drugs) can ultimately be used in analytical tests predicting drug therapeutic interventions (Knapik et al., 2019; Kirubakaran et al., 2018). Since the gut microbiome and their xenobiotic activity plays crucial role in host therapy, it is valuable to understand personalized microbiome through mNGS approach. Indeed, the understanding of gut microbiome and host interactions through mNGS and metabolomics leads to development of novel drugs, biomarkers and therapeutic strategies (Spanogiannopoulos et al., 2016). Taken together, understanding the xenobiotic activity of in vivo and environmental microbiome through the metagenomic approach will benefit clinical and industrial research respectively.

3.5. Industrial components

The impact of metagenomics in industrial components is increasingly recognized in the agrochemical, pharmaceutical and several other industries. Metagenomics revolves around two categories: (i) production of secondary metabolites as bioactive products by microbial biocatalysts and (ii) synthesis and development of enzyme system from novel genes or gene clusters (Wong, 2010; Yashir et al., 2014; Ufarte et al., 2015). Industries are keen in uncultivated microorganisms to explore the knowledge that has been identified through large-scale environmental genomics for several reasons including efficiency, economical, more suitable biocatalyst, novelty, maximum diversity and elusive metabolites (Lorenz and Eck, 2005). Metagenomics promises to provide new molecules with diverse functions, the biocatalyst operating system with high efficiency, the detergent additives, bioactive compounds, fuels (alcohol, biodiesel), chemical intermediates for chemical and drug synthesis (Curtis et al., 2002; Ward, 2002; Schloss and Handelsman, 2004). Various other industrially important enzymes produced through metagenomics are cellulases, lipases, xylanases, amylases, proteases etc., (Nazir, 2016; Lorenz et al., 2002; Coughlan et al., 2015; Kang et al., 2011) (refer Table 1). There are many examples in the literature where metagenomics has facilitated the process of degradation of toxic industrial pollutants and other components (Leigh et al., 2007). For example, polychlorinated biphenyls, a synthetic aromatic compound, a component of adhesives and plastic materials widely used in the electronics industry and an organophosphorus insecticide, chlorpyrifos (3,5,6-trichloro-2-pyridinol (TCP)) which is widely used for crop protection have been degraded using the enzymes derived from metagenomic approach (Mukhopadhyaya et al., 2010; Uhlik et al., 2013).

3.6. Clinical approach

Metagenomic approaches have been applied in various niches, ranging from the complex macroenvironment to human microbiome (Lavezzo et al., 2016; Samarkos et al., 2018). Metagenomic studies became increasingly accessible in the clinical settings with the advent of Next Generation Sequencing (NGS). NGS can be used with two different approaches: targeted metagenomics, focusing on a specific target region or shotgun metagenomics, non-specifically amplifying all the sequences in a sample (Nakagawa and Fujita, 2018; Chiu and Miller,

2019). The clinical approach of metagenomic next-generation sequencing (mNGS) can help us to evaluate the comprehensive whole microbial community (Viruses, Bacteria, Fungi and Parasites) and their genetic material (DNA and RNA) in the host organisms (Chiu and Miller, 2019). The emerging mNGS approach changes the whole perspectives of diagnosis and treatment of infectious diseases. Indeed, the technique is effectively used to study the antimicrobial resistance, clinical microbiome, human host response and also if applicable, in oncological sciences to extract the viral genome information (Human Microbiome Project Consortium, 2012; Rastogi and Sani, 2011). For example, alterations of the microbiome, known as dysbiosis, had shown to be related to obesity, diabetes mellitus and inflammatory bowel disease and manipulation of the microbiome might be a route to treat these conditions, which can be achieved by mNGS method (Chiu and Miller, 2019; Boulange et al., 2016; Palmer et al., 2006). Moreover, in oncology, whole-genome or directed NGS approaches identify the mutated genes and can be used simultaneously to uncover viruses associated with cancer (that is, herpes, papilloma and polyoma) and its host interactions through metabolomics study (Lefterova et al., 2015; Rota, 2003; Sotiriou and Pusztai, 2009; Samarkos et al., 2018). Some early successes using this technology include, the discovery of the SARS coronavirus genes, profiling of mutations in cancer and in-depth microbiome analysis of different sites in the human body (Chiu and Miller, 2019).

4. Conclusion

Metagenomics an amalgam of genomics, structural biology, microbial biotechnology and genetic engineering investigates the illimitable environmental benefits of uncultured microbes. The discovery of bioactive substances using metagenomics has given the bioremediation, enzyme industries, and clinical diagnosis new directions. Further advancement in metagenomics can enable humans to create a sustainable world, balancing ecosystems, improve agricultural production, and their productive bioremediation systems. Clinical metagenome is a promising approach to effective diagnosis and personalized treatment. Metagenomics will be used successfully in environmental and clinical monitoring. Furthermore, clinical metagenomics and metatranscriptomics with metaresistomics enable to estimate pathogens pharmaceutical resistance and develop successful therapeutic strategies.

Author contribution statement

Rangasamy Kirubakaran -Writing and Editing; KN Arul Jothi - Writing and conceptualization; Sundaravadivel Revathi - Writing and literature search; Nowsheen Shameem - Data collection and reviewing; Javid A. Parray Draft preparation and Final Editing.

Declaration of competing interest

The authors declare that they have no conflict of interest and no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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