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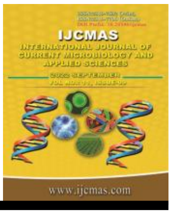

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Exomicrobiology: The Effects of Outer Space and its Potential Scope for Mankind

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ABSTRACT

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Ever since the early days of space exploration and research, studies related to the survival of life in the outer space has gained much of momentum. As time passed, the advancements in the technology have given us the ability to develop advanced facilities to study and dive deeper into the responses of microorganisms to the stress conditions existing in the space. After the Theory of Panspermia was proposed by Swedish scientist Svante Arrhenius and later by Sir Fred Hoyle, it's been almost half a century that the research related to microbial behavior in space has begun and is still continuing. The International Space station has been the regular site which functions as the observatory for understanding the effects of space related factors such as Microgravity, Radiation, Vacuum etc. on microorganisms. Their adaptability and survival have always been the keen area of interest along with to identify the mechanisms carried out by predominant species in these extreme conditions. These adaptations can be either useful or be dangerous for both the spacecrafts as well as the crew members onboard. Therefore, it is necessary to monitor and study how the conditions like radiation and microgravity could influence the microorganisms. Advanced techniques in -omics studies have helped in genomic level research of microorganisms exposed to space conditions. Addressing these microbial alterations will help in designing the counter measures to their damaging effects and allow us to utilize their properties that are potentially useful. Various processes are hence being studied in both *in situ* and *ex situ* environments. In this review we will also discuss how these researches would be stepping stones for sustenance in the future longer manned space missions to Mars and beyond.

Introduction

The outer space is an extreme environment which poses a great challenge for the survival of life of any sort. The outer space is cold, immense in size and is continuously under radiation. Ever since the earth has evolved for more than 4 billion years, it has protected us from these hostile conditions. It's been more than half a century of extensive research and development in the field of space technology, which has enabled us to study the on-site effects of these hostile conditions on life beyond the safe zones of earth (Horneck *et al.,* 2010).

Every year, the earth receives more than 10^{18} live cells from the outer space in the form of deposition on various comet particles that lands up in the earth's atmosphere. This theory of Panspermia has paved the way for probing how microorganism could survive in the extreme environments of the outer space (Hoyle *et al.,* 1999). Early biological experiments with microorganisms involving viruses, bacteriophage, unicellular organisms like bacteria were conducted in balloon flights and various unmanned and manned spacecrafts like STS and Soyuz missions. Now the international space station hosts various microorganisms that are contaminants, which are used in experiments and which are present in the natural microbiota of the crew onboard (Dickson, 1991; Venkateswaran *et al.,* 2014).

The first experiment to study about the extent of survival of the microbial life in the *in-situ* space condition was done during the Gemini 9 and Gemini 12 mission of NASA in 1966. This experiment directly exposed T1 bacteriophage and spores of *Penicillium roqueforti* to the outer space conditions like UV rays and X rays for 16 hr and 6 hr and they could successfully survive (Hotchin *et al.,* 1968).

Investigation and analysis of the economically important microbial life to the space conditions will give us more knowledge about how to efficiently engineer and utilize their production of important compounds (Blachowicz *et al.,* 2019).

Some microorganisms which are otherwise commensal in nature can turn into pathogens when exposed to the space conditions (Klaus and Howard, 2006).

It is a known fact that the microorganisms change their physiological and genetic composition to adapt to the stressful environment, so does in the environment of the International Space Station (Horneck *et al.,* 2010).

Several microorganisms which were isolated from the Space Station consisted of both commercially important microbes as well as pathogens (ChecinskaSielaff *et al.,* 2019).

Analyzing these adaptations will help us to design various strategies to reduce the risk factor posed by pathogenic microbes so that future spaceflights and stay at the ISS can be made safe (Taylor *et al.,* 1997). This could help us in implementing more safer measures for long-term space flights and manned space exploration missions.

Effect of Outer Space Environment on Microbial Life

Microgravity

The international space station (ISS) revolves around the earth at an altitude of 400km in the thermosphere layer of the Earth's atmosphere and has a stable orbit known as the Low Earth Orbit (LEO) (Castro *et al.,* 2013).

Hence, in the LEO, the microorganism will undergo tremendous stress conditions. They will experience low gravity (10^{-3} to 10^{-6}g), low pressure (10-7 to 10-4 Pa) and a long range of variable temperatures (153 to 393 K). The LEO also consists of ionizing radiations such as galactic cosmic radiation (GCR), solar cosmic radiation (SCR), and also a radiation belt trapped by the magnetosphere of the earth (Horneck *et al.,* 2010).

The majority of the study and experiments on the Space Station are carried out in pressurized space capsules equipped with life supporting systems. Therefore the microorganisms are protected from the extreme most conditions with exception of micro gravity and cosmic radiations. Hence, we can conclude that most differences observed will be on the basis of these two factors (Senatore *et al.,* 2018).

The other external factors would be considered if the study was particularly done outside the environment of the ISS. Herethe term microgravity refers to the phenomena of weightlessness caused because of the less force exerted by gravity, but it is never zero (Horneck and Zell, 2012; Nickerson *et al.,* 2004).

From the experiments it was concluded that one of factor that affected the microbial life because of microgravity was their motility (Benoit and Klaus, 2007). Regarding the non-motile cells, the affected factors because of microgravity were observed as reduction in lag phase and increase in cell density as compared to that of earth conditions (Zea *et al.,* 2017).

This was found out with a fact that the fluidity around the non-motile cells remains inactive which results in less nutrient uptake and reduced metabolism. This could have caused because of change in the chemical composition of the cell. On the other hand motile cells exhibited better mass transfer due to flagellar movements (Thévenet *et al.,* 1996).

Some of the microorganism like *Escherichia coli* exhibited increased resistance to drug in microgravity because of increased membrane fluidity but *Pseudomonas aeruginosa* did not show any change in membrane fluidity at all (Baker *et al.,* 2004; England *et al.,* 2003).

From this it is evident that effect of microgravity shows a variety of effects on microorganisms. A study showed increased rate of plasmid exchange in gram positive bacteria under these space condition, which might help them to adapt to these stress conditions of space (De Boever *et al.,* 2007).

Another study on *Salmonella* under microgravity showed that expression of about 100 genes were altered which included transcription factors, virulence factors, enzymes for synthesis of various products etc. (Wilson *et al.,* 2002).

Cosmic Radiation

The second factor that affects the microorganism along with microgravity are the Cosmic Radiations. These radiations can induce mutations and influence the microbial metabolism either through indirect interaction of radiation particles with the biomolecules or through the direct energy absorption by the biomolecules (Huang *et al.,* 2018).

In addition to these, experiments with *E. coli*, *B. subtilis* and *D. radiadurans* showed that DNA is damaged because of the radiation, causing breakage in the double strand which leads to mutations (Micke *et al.,* 1994; Schafer *et al.,* 1994; Zimmermann *et al.,* 1994).

The DNA repair mechanism of microorganisms plays a crucial role in how efficiently they can tolerate the radiation. They carry out this phenomenon by homologous recombination or by joining non-homologous ends. Microorganism *D. radiodurans* was found 5 times more resistant than the spores of *B. subtilis* on its exposure to the space radiation. Hence, it was clear that the ability to repair DNA and the resulting mutations were responsible and the key for the survivability (Senatore *et al.,* 2018).

Apart from the DNA, other biomolecules like proteins and lipids also get altered when they are exposed to cosmic radiations and other radiations like UV and Solar radiations, as a result of which reactive oxygen is produced, causing the damage (Senatore *et al.,* 2018).

Some fungal species and spores where also found to be radiation resistant along with bacteria.

When exposed to UV- C radiation, some fungi could show enhanced UV resistance than the *Bacillus* endospores (Blachowicz *et al.,* 2019).

These increased mutations played a crucial role in the survivability of the microorganism as they altered various pathways of metabolism in them.

Adaptations of Microorganisms in Space Conditions

It is now evident that Microgravity and Cosmic radiation could seriously affect various microbial processes such as gene expression, growth, virulence, drug resistance etc. (Baker *et al.,* 2004; Demain and Fang, 2001; Kacena *et al.,* 1999; Kim *et al.,* 2013).

This is due to the reduction of uptake of nutrients (mass transfer) causing the change in the metabolism due to low gravity (Zea *et al.,* 2016). Thus, the study of the phenomena like drug resistance, increased virulence activity and alterations in the production of secondary metabolites, resulting in giving out greater quantities of industrially important compounds or even newer compounds is of a huge scope (Wilson *et al.*, 2007; Benoit *et al.,* 2006; Lam *et al.*, 2002).

Drug Resistance

Experimental studies have shown different expression of responses to stress conditions in microorganisms in the outer space conditions, the drug resistance phenomenon being among the prominent ones. Altered drug resistance is a matter of great concern as it affects the health and well-being of the crew members on board a spacecraft.

Studies on bacteria like *E. coli* and *S. aureus* showed that they were more resistant to all antibiotics tested in space conditions as compared to the ground tests (Lapchine *et al.*, 1986).

Apart from the drug resistance, *E. coli* and *S. typhimurium* which were grown in microgravity showed better resistance to thermal stress, osmotic stress and greater ability to survive in macrophages (Lynch *et al.*, 2004).

In *E. coli*, analysis showed that 50 stress response genes were upregulated in the microgravity conditions (Aunins *et al.*, 2018).

Studies also showed the greater probability of horizontal gene transfer in mostly gram-positive bacteria, giving them the drug resistance capacity. It was found that plasmid borne erythromycin and tetracycline genes were horizontally transferred from *Staphylococci* (Vaishampayan and Grohmann, 2019; Sobisch *et al.*, 2019).

B. thuringiensis also showed greater antibiotic resistance and virulence because of the higher chances of the horizontal gene transfer (Beuls *et al.*, 2009).

Virulence Factor

Pathogenic organisms like *P. aeruginosa*, *A. fumigatus* and *Fusarium oxysporum* showed alteration in regulatory signals in the space conditions, which lead to changes in expression of genes and enhancing their pathogenicity. This increased levels of virulence and pathogenicity could be a threat to the crew members on-board long-distance spaceflights with compromised immunity and hence it is crucial to identify their mechanisms and virulent strains (Crabbé *et al.*, 2010; Knox *et al.*, 2016; Urbaniak *et al.*, 2019).

In the studies and isolations conducted at the ISS, the isolated *A. fumigatus* were found more deadlier than the ones in clinical trials in ground conditions (Knox *et al.*, 2016).

Drosophila infected with pathogen *Serratia marcescens* at the ISS were found to have significant shorter life span as compared to the control. In other microorganisms like

C. albicans, the transition into its hyphal form in microgravity showed virulence (Gilbert *et al.,* 2020; Altenburg *et al.*, 2008).

Therefore, above it’s clear that how important it is to address the pathogenicity and virulence of microorganisms in space for having safer long- term space missions.

Secondary Metabolites Production

It is evident from the above facts that there is significant effect of microgravity on the growth and metabolism of the microorganisms (Taylor, 1974).

The importance of the secondary metabolite production is of greater interest because of their biotechnological evidences. Many experiments that were carried out in the space and in the simulated environment on ground, showed excess production of secondary metabolites in the microbes that were pharmaceutically important than the normal earth conditions (Blachowicz *et al.*, 2019; Knox *et al.*, 2016; Romsdahl *et al.*, 2019).

The secondary metabolite production generally increases in the space conditions. Studies on *Humicola fuscoatra* samples on the STS- 77 mission showed higher production of Monorden antibiotic when compared to the ground conditions (Lam *et al.*, 1998).

Similarly, *Streptomyces plicatus* showed increased production of Actinomycin D antibiotic in spaceflight conditions (Lam *et al.*, 2002).

Microorganism *Aspergillus fumigatus* isolated from ISS showed production of novel metabolites of industrial importance, with increased production of Fumigaclavine A which is an antibacterial compound.It was later found out that Frame shift mutation caused these increased Fumigaclavine A production (Knox *et al.*, 2016).

Other *Aspergillus* species like *A. nidulans* and *A.niger* isolated from ISS produced significantly more amount of Asperthicin, an anthraquinone pigment and antioxidant Pyranonigrin (Romsdahl *et al.*, 2020).

These studies indicate that the increased amount of production of these metabolites may act as a protection for these fungi from the space radiations and also how space conditions would be helpful in recovering these commercially important metabolites.

Even after many positive results, many other studies have shown that the microgravity can affect inversely in the secondary metabolite production. In *Streptomyces hygroscopicus*, Rapamycin, which is an immunosuppressive drug, was reduced by almost 90% as compared with the normal conditions (Fang *et al.*, 2000).

Benoit *et al.*, (2006) interestingly pointed out that the enhanced Actinomycin D production in *S. plicatus* was seen between 8-12 days in microgravity, but the ground control production surpassed it for the rest of the mission.

These prolonged experiments indicated that the activation of specific pathways and production of secondary metabolites by the microorganism could be a time bound activity.

Formation of Biofilm

Under the extreme space conditions involving microgravity and cosmic radiation, the formation of biofilm was first seen in microorganism *P. aeruginosa* (McLean *et al.*, 2001).

Also, other studies have shown that microorganisms forming biofilm on surfaces of spacecrafts, on its water systems could be dangerous to the health of the crew on board or it may cause corrosion of the surfaces making it vulnerable to disasters (Novikova, 2004; Song and Leff, 2005; Gu *et al.*, 1998).

The water systems including pipes, air conditioners, recyclers, electric connectors were the prime spots where these microbial growths were observed (Novikova *et al.*, 2006).

Out of all the microorganisms forming the biofilms, more of the polymer biodegradation were shown by the fungal species (Novikova, 2004).

Bacterial species like *Sphingomonas, Methylobacterium* and other coliforms were also found in the drinking water and wastewaters of the space station (Novikova *et al.*, 2006; Koenig and Pierson, 1997).

Studies have indicated that the biofilm formation in microorganisms could be due to increasing cell clumping, enhanced production of extracellular matrix as a result of the extreme space conditions. Hence, the focus of construction of future spaceflights should be given in making it less microbial biodegrading and biofilm resistant (Wilson *et al.*, 2007; Zea *et al.*, 2018).

Changes in Natural Microbiota of the Crew on Board

We are aware that the microbial life is also an integral composition of the human body and it could also get affected due to the exposure to space conditions. Apart from the adverse effects on human health, microbes are also helpful for us in many ways. Studies related have shown that space conditions have enhanced the growth of microorganisms in the Gastrointestinal (GI) sample taken from the crew members, but their diversity was considerably decreased (Taylor *et al.,* 1971).

Samples from the nasal, oral and gastrointestinal areas showed significant difference in the microbial count in the outer space environment. (Brown *et al.,* 1976; Decelle and Taylor, 1976)

The increased amount of pathogenic bacterial species was also seen to show more rate of transfer amongst the crew members. Some of the crew also reported allergic tendencies in the environment of the ISS which might have caused due to prolonged exposure to some fungal pathogens (Venkateswaran *et al.,* 2014; Lencner *et al.,* 1984).

Studies have also showed that the reduction of the natural microbiota of the human body might be due to the limited and confined diet and lifestyle of the crew members (Hao *et al.,* 2018).

The natural microbial diversity of the human body can have very considerable effect on the immunity, immunity responses and healthy conditions of the body (Heyde and Ruder, 2015; Siddiqui *et al.,* 2021). So, it is important to maintain a healthy microbial composition in the crew members to avoid diseases if their immunity is compromised.

Future Prospects of Study and Applications of Microorganism in Missions to Mars and Beyond

With the advanced study of omics, it has become possible of for us to isolate and identify the novel species of microorganisms in the space conditions (Bijlani *et al.,* 2021; Venkateswaran *et al.,* 2017). The use of Genomics, proteomics, transcriptomics and metabolomics has helped us in understanding the variety of microbial life in the spaceflight conditions. Using the shot gun sequencing technique, we could study the diversified composition of microorganisms at different time in different areas in the space conditions (Checinska *et al.,* 2015).

Studies like metagenomics have helped us in concluding the presence of *Klebsiella pneumonia*e in the ISS at different point of time. It also has aided in understanding their virulence factors and genes of antimicrobial resistance which could be controlled with the ground conditions (Singh *et al.,* 2018).

Analysis of transcriptome, proteome and genome have paved the ways for understanding which proteins were responsible for the adaptations of microorganisms like *A. fumigatus* to space conditions, its stress responses, secondary metabolism etc. (Blachowicz *et al.,* 2019).

All in all, the advancements in the omics have led us to establish a relation between the phenotypical and genotypical responses in the microbial life in outer space environment. This will help us to develop precautionary remedies to pathogenic microorganisms and provide safer manned space flights to mars and beyond in future (Schmidt and Goodwin, 2013).

The curiosity regarding the changes in the interaction between the microorganisms, their pathogenicity, adaptations with other species have revealed us the secrets of microbial life in space conditions (NASA, 2016).

Despite the pathogenicity of microorganisms are a matter of concern the future studies should be focused more towards how beneficial they can be in life supporting processes, how they can be utilized in the waste degradation, waste recovery, oxygen production etc. (Acevedo-Rocha *et al.,* 2019; Carillo *et al.,* 2020).

Studies carried out using certain fungi, bacteria and cyanobacteria were found to produce enhanced vitamins, recycled water, managed wastes, degraded plastics and decontaminated air in the space environment (Roberts *et al.,* 2004; Cortesão *et al.*,).

Therefore, the best possible solution is to balance out the microbial flora to minimize the detrimental effects on spacecrafts and crew members and maximize the life supporting processes.

Development of vaccines and against pathogenic organisms like *Salmonella* which causes diarrhea and new therapeutic drugs for treatment in space environments will help us to carry out the same for the use at ground levels where organisms experience the same conditions. Viruses may be dangerous to the crew, but live attenuating these viruses and production of vaccine slow and cease the bacterial growth that are dangerous (Higginson *et al.*, 2016; Horneck *et al.*, 2010).

In general, we could see that how microbial life responds to the space environment, how they can be both detrimental in space conditions as well as how efficiently we can exploit their benefits. Numerous studies and tests were carried out and are being carried out on how the potential of microorganisms can be harnessed for the benefits of human for our long spaceflight missions. Advancement in technologies, advent of -omics have given us a better idea on various changes and have revealed how outer space stress conditions can affect the microbial life and how they respond to it. It is the left to us to develop newer techniques and strategies for sustaining the human life in a healthy manner in future manned long-term missions (Bijlani *et al.*, 2021).

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