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Relevance of Microbiome and Biofilms in The Development of Cancer

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In the present review, we have reported the microbiome and biofilms role in the development of cancer. Understaning the role of host microbiome in promoting the cancers like Pancreatic, Breast, Lung cancers, Melanoma and leukemia is essential for effective treatment and has been discussed in the review. We also discussed the microbiome's role in therapeutic effect. It includes the methods through which the microbiome can be identified in different cancer patients. The role of Phage display technology for inhibiting the cancer development has been discussed.

ABSTRACT

The harmonious relationship between human well-being and disease is increasingly relyingon the microbiome. Evaluating the intricate connection between the cancer and microbiota has been substantially Increasing in day- to-day life ensuringas a result of recent scientific advancements. There isan evidence that, the microorganismsperhaps increased the person's risk chancesand also develop certain types of cancer besides that may also havethe impactthat, howdoes they react towardsindigenous treatment methods. The current evidencessuggest that, altering the microbiome may change the molecular reactions in order to transform variety of therapy's in terms of cancer which is highlighting its importance in response to treatment. The inhabitant microbiota plays a significantpart in quickening and directing the gene expression in hostimmuneresponse. Although the microbiome influences the developmental mechanisms which are not related to inflammation as well as to the immune function, that promotes the relationship between microbial community and cell tropism is the most well-known factor to be consider.But Immunologic dysregulation may provide molecular alterations & howbest the microbiome promotes tumourprogression and for counter therapy. To understand and realize potential methodologies, it is essential to have a magnanimous understanding the interrelation between biofilms ofhost microbiome, immune responses and cancer. In the current review, we highlighted the microbiomes associated with cancers and their response towardsdifferent therapies.

Keywords: Microbiome and biofilms, Tumourmicrobiome, Oral microbiome, Immunotherapy, Phage display.

INTRODUCTION

Bacterial biofilms are a sort of microbes that create an extracellular framework by adhering to both biotic and abiotic surfaces. The majority of the biofilms are harmful to human health[1]. Extracellular matrix is an essential for bacterial motility, differentiation, and protection against the host immune system and antimicrobial drugs. *Pseudomonas aeruginosa*, a gram-negative and a prominent biofilm inducer is known to produce three distinct exopolysaccharides[2].

After the stomach, the second-largest microbial community, with approximately 700 species of bacteria, protozoa, viruses, and fungi, is believed to be found in the oral cavity[3]. The pH of saliva, teeth, tongue, soft and hard palates, and tonsils all serve as favorable environments for nutrition delivery to bacteria and microorganism growth[4].Previous research has connected various health issues and diseases, such as dental caries, stroke, and cancer, to factors such as poor food, lifestyle, and an imbalance in the microbiomes found in the mouth cavity[5].Under selective pressure, microbes express antibiotic resistance genes for survival and genetic perseverance by increasing resistance to different antibiotics[6]. Because antibiotic therapy is less effective against biofilms, an alternative therapy called phage therapy, whichever is particularly successful against oral infections, is being

considered[7].Cancer is a devastating disease that claims more lives worldwide than any other cause. Genetic, environmental, or epigenetic alterations in cells can lead to the development of cancer. It is imperative that we continue to support research and advances in cancer treatment to reduce the impact of this deadly disease. Biological factors play a role in causing cancer. Globally 16–20% of malignancies are caused by microbes. Inflammation and immunosuppression brought on by commensal organisms can transform into pathogenic infections under the right circumstances, increasing the chance of developing cancer.Additionally, microbiomes may affect later medical procedures that manage the side effects of chemotherapy[8].

Cancer treatment remains a challenge because of its high resistance and lack of specificity, which makes it difficult to diagnose the disease. Early signs are neglected in some types of cancers like prostrate, pancreatic, and esophageal cancer which become difficult to diagnose[9].

Here, we provided information on bacterial biofilms and their impact on cancer development. We focused on the oral microbiome's link to the emergence of several malignancies. The findings and the oncogenic mechanism of bacterial biofilms, which are assumed to be the link with the emergence of various cancers, are both thoroughly described in this paper. This study's primary goal is to provide insight into the microbes connected to the emergence of various malignancies. It also discusses how phages can treat cancer.

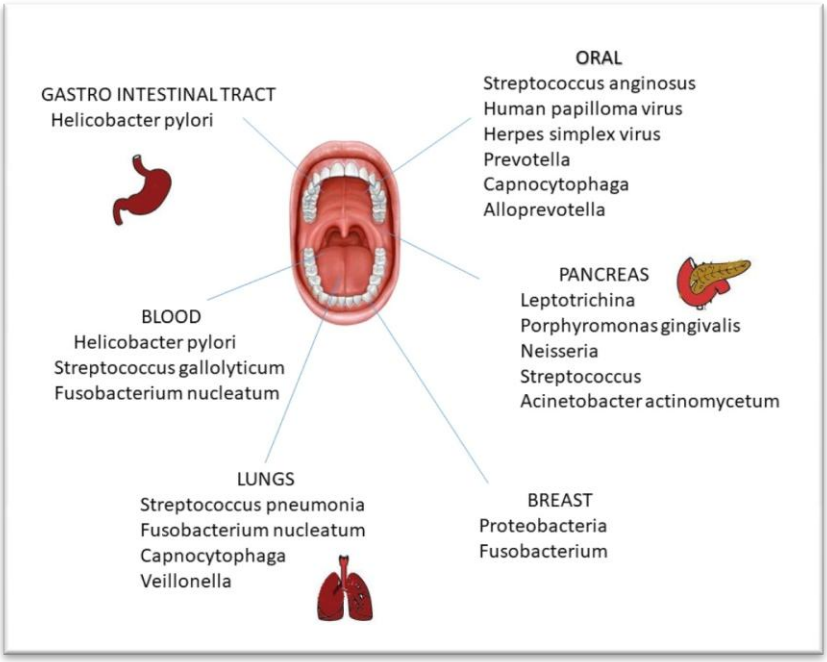

Fig:1 Oral microbiome related to different cancers

Microbiome and Pancreatic cancer

The pancreas, which is a sterilized organ, was found to have a large number of germs. The bacteria in the mouth and gut that trigger pancreatic cancer are different in healthy persons from those who have the disease[10]. To analyze the tumor microbiome, Nijman et al. (2020) examined 1010 distinct tumors and 516 control samples and found that pancreatic cancer had the greatest proportion of tumors that were positive for bacterial DNA. Proteobacteria was the dominant microbe although *Fusobacterium nucleatum* is primarily found in colorectal, breast, and pancreatic cancer patients[11]. Mirji et al. (2022) studied the combination of immune checkpoint blockade and the metabolite trimethyl amine N-oxide produced by the gut microbiome in a mouse pancreatic tumor model, which had therapeutic effects (anti-PD-1/anti-TIM-3) enhanced antitumor immunity correlated with immune-stimulatory tumor-associated macrophages, and enhanced the type 1 interferon pathway and effector T-cell response in the tumor microenvironment[12].According to Soloman et al. (2003) analysis, PC and tooth loss were substantially related[13].

According to Michaud et al. (2013), individuals with elevated levels of antibodies to Porphyromonas gingivalis exhibit a lower risk of developing pancreatic cancer compared to those with increased levels of antibodies to other common oral bacteria. These findings suggest that increased levels of antibodies to specific oral bacteria may affect an individual's likelihood of developing pancreatic cancer.However, he did not discover a connection between tooth loss and pancreatic cancer, although they did discover an elevated risk in those patients[14]. Several serological and cultural approaches were employed to establish the connection between *Helicobacter pylori* found in tooth plaques and pancreatic cancer[15].Nevertheless, several recent studies were unable to conclude an association between

Helicobacter pylori and pancreatic cancer because the majority of commensal microorganisms found in the oral cavity cannot be cultured, making analysis of their contribution to cancer development difficult[14,15]. Swidsinki et al. (2005) observed dense biofilms attached to the pancreatic canal in three biopsy studies in patients with calcified pancreatitis[16]. Vogtmann et al. (2020) reported that order Enterobacteriales and genus Lachnospiraceae were highly associated with pancreatic cancer patients, whereas Haemophilus was more abundant in control[17].

Microbiome and lung cancer:

Saliva, due to its ease of collection and storage, plays a significant role in the early identification of several diseases, including pancreatic, lung, breast, gastric, and oral cancers. It is also used as a monitoring tool in a variety of scientific fields[18]. EFIRM (electric field-induced release and measurement), a new technique created by Wei et al. (2014), is used to identify epidermal growth factor mutations, most frequently found in non-small cell lung carcinoma and epithelial malignancies. Saliva can detect tumor-shedding exosomes, microRNAs, tumor-specific proteins, and mRNA, resulting in the development of a new noninvasive detection technique[19].In NSCLC therapy, Qian et al. (2022) discovered a correlation between *Prevotella copri* nervonic acid, all-trans-retinoic acids, and CD-14; however, the mechanism by which *Prevotella copri* affects nervonic acid is yet unknown[20].

Elevated levels of Lachnospiraceae, Peptostreptococcaceae, and Parvimonas microspecies have significantly reduced the risk of lung cancer[21].Vogt Mann et al. (2020) discovered that the oral microbiota is connected to the occurrence of lung cancer, particularly squamous cell carcinoma, and former smokers. A high alpha diversity reduces the incidence of lung cancer. Abiotrophia, Streptococcus or Lactobacillus, and detectable Peptoniphilus, in contrast to *Aggregatibacter* and *Eubacterium Yuri*, have all been connected to a higher risk of lung cancer[17].Yan et al. (2015) analyzed squamous cell cancer (SCC) and adenocarcinoma (AC) patient samples using 16S rRNA sequencing and identified Veillonella and Capnocytophaga as promising biomarkers for SCC and AC diagnosis, respectively. Neisseria was discovered at lower levels in SCC, AC, and pancreatic cancer patients than in control studies, indicating that it prevented cancer cell proliferation[22,23]. Salivary microbiome dysbiosis was discovered in nonsmoking female lung cancer patients. Fusobacterium may produce pathogenic factors in the oral microbiome of cancer patients[24,23]. Nivolumab, an immune checkpoint inhibitor that targets PD-1, reduces the risk of death in lung cancer patients by 40%[25].

Microbiome and breast cancer

Breast cancer has been correlated with several risk factors, including family history, obesity, and hormonal replacement therapy. But recent studies observed a correlation between microbiome and breast cancer.Obesity significantly increases the risk of developing premenopausal triple-negative breast cancer by 67%, as people with elevated adipose tissue produce more adipokines and inflammatory cytokines that increase the concentration of estrogen, which contributes to estrogen receptor-positive breast cancer progression[26].Anticancer drugs, coupled with inhibitors such as sodium butyrate and other histone deacetylases, show potential in the treatment of triple-negative breast cancer[27].According to Plottel and Blaser (2011), changes in hereditary and environmental modulators impact the bacterial composition of the Estrobolome, and its movement can hence lead to raisedamounts of circulating estrogens and their metabolites, improving the chance of cancer advancement[28].

By comparing the gut microbiomes of breast cancer patients and healthy women, Minelli et al. (1990) revealed intestinal microbiota as an alternate metabolic source for estrogens in breast cancer patients. Bacteroides, Clostridium, and Enterobacterium were found in high concentrations in breast cancer patients[29]. Dysbiosis in the gut microbiota is linked to postmenopausal breast cancer but not to premenopausal breast cancer[30]. Goedert et al. (2018) investigated whether there are substantial estrogen-independent relationships between breast cancer cases and IgA-positive and IgA-negative gut microbiota[31]. Ma and Sun et al. (2020) discovered a breast cancer detection method that uses flora metabolites in combination with flora bacteria (*Faecalibacterium* combined with phosphoryl choline) to suppress the growth of breast cancer cells by inhibiting the IL-6/STAT3 pathway, which aids in the prevention of breast cancer[32].

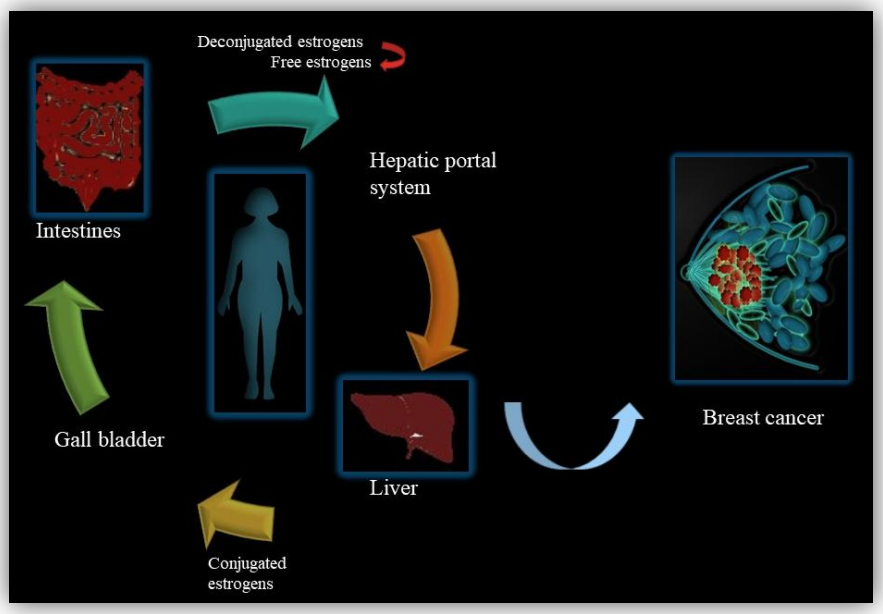

Fig:2 Estrogen receptor dependent breast cancer

Microbiome and Leukemia

With a rise in invasive fungal infections, morbidity and mortality in acute leukemia rise. The fungi Candida, Fusarium, and Aspergillus are linked to acute leukemia. Acute myeloid leukemia patients with neutrophil depletion also have invasive fungal infections[33]. In a longitudinal cohort study, Robinson et al. (2020) found that RIC (remission induction chemotherapy) affects the oral microbiome in individuals with acute myeloid leukemia. The results of bacterial infections are correlated with changes in the populations of Candida and Fusarium[34].A high-risk factor in leukemia patients may be the growth of opportunistic microorganisms. In their investigations, Wang et al. (2014) found that ALL patients are more likely to develop systemic infections when there are imbalances in the oral microbiota. He observed abundant changes in phyla Firmicutes and Fusobacterium in leukemia patients[35].Smith et al. (2022) conducted their studies to analyze the part of the intestinal microbiome in reaction to CD19- focused on CAR-T-cell treatment by performing 16S rRNA and metagenomics shotgun sequenceanalysis. A relative abundance of Bacteroides and Bifidobacterium was observed in CAR-T-cell patients[36].Yamamoto et al. (2013) observed that the plethora of Lactobacillus johnsonii may cause the development of delayed B-cell lymphoma by orally administering*Lactobacillus johnsonii* in a mouse model.L.johnsonii enhanced the anti-inflammatory cytokines TGF- and IL-10 while decreasing the proinflammatory cytokines IL-1 and IFN, demonstrating the relationship between gut microbiota and systemic inflammation[37]. More research is required to determine whether the gut microbiota influences human immunity and, thus, contributes to the emergence of acute leukemia.

Microbiome and Melanoma:

The most lethal type of skin cancer, malignant melanoma, accounts for around 1% of all skin malignancies and emanates from epidermal melanocytes. The gut microbiome is involved in either pro or antitumorigenic roles and acts as a biomarker in response to chemo and immunotherapy[38].Vitali et al. (2022) discovered a combination of gut fungal and bacterial profiles connected with melanoma invasively in their investigation into the extent to which the gut microbiome influences melanoma. While some fungal communities set off proinflammatory reactions and aid in melanoma regression by inducing systemic immune responses, bacterial and fungal community correlation leads to melanoma invasiveness[39]. A Melanocytic protein receptor (MC1R), a seven-pass transmembrane protein, regulates skin pigmentation, melanin synthesis, and hair color via several proteins such as agouti signaling protein and melanocortin[40].Inamdar et al. (2010) targeted the MAPK/ERK pathway, which is involved in melanoma progression, using a variety of downstream proteins such as RAS, RAF, MEK, and ERK[41]. Inosine, a modulator, created *Bifidobacterium pseudolongum* and *Lactobacillus johnsonii* by promoting Th1 differentiation via the A2AR- cAMP- PKA pathway to boost T-cell antitumor capabilities[42,43]. Immunotherapy medications like PD-1 and PD-L1 are successful cancer treatments, but novel techniques like fecal microbiota transplantation, which reprograms the gut microbiome, may change the microenvironment of tumors.Davar et al. (2021) examined this by combining fecal microbiota transplantation with anti-PD-1 treatment in people with PD-1 refractory melanoma. FMT and anti-PD-1 treatment changed the intestine microbiota and tumor microenvironment by upgrading CD8 T-cell activation and declining the IL-8-expressing myeloid cells[44].Advanced research progresses our understanding of microbial interactions and their regulation as a therapeutic technique in cancer treatment.

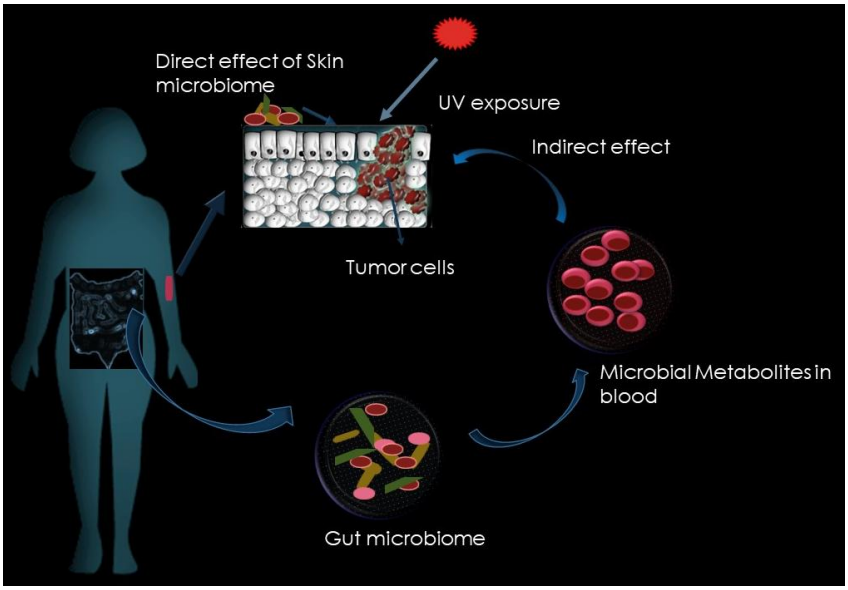

Fig: 3 Modulation of gut microbiota in cancer development

Table 1: Overview of recent clinical studies investigating the role of themicrobiome in cancer development

Type	Type of sample	Age and Patients Sample	Methods	Microbiome	Conclusion	Ref
Pancreatic cancer	Saliva	Above 18 years P=41 C=69	16S rRNA gene sequencing And statistical analysis by SPSS software	High risk of PC is caused by increased Z scores for Streptococcus and Leptotrichina.Veillonella and Neisseria Z scores dropped, lowering the risk of PC	Salivary microbiomes of PC cancer patients and healthy individuals both had significant modifications.	10
	Saliva	P=273 C=285	16S rRNA gene sequencing and MiSeq	Order Lachnospiraceae and enterobacteriales were strongly linked to PC	The microbial communities of PC and control patients were different.	17
Lung cancer	Saliva	P=10 C=10	Deep sequencing analysis and 16S rRNA analysis with qPCR.	Neisseria, Veillonella, Capnocytophaga, and Selenomonas were all widely distributed.	Veillonella and Capnocytophaga concentrations were greater in the patients' saliva.	23
	Blood and Saliva	Mean value 59.49 P=39 C=20	16S rRNA amplification and sequencing	Streptococcus, Veillonella, and Leptotrichia are widely distributed.	Fusobacterium and Prevotella species were decreased, while the phylum Fermicutes and its genera were more numerous in patients than in controls.	45
	Breast cancer tissues	NA P=148 C=20	Pathochips array design	Firmicutes and proteobacteria are prevalent in some cases.	There are bacterial, fungal, viral, and parasitic microbiomes. In all patients of breast cancer with endocrine receptors, the parapoxviridae and poxviridae families are present.	46
	Blood and	25 to 75years	ELISA	Staphylococcus aureus and	Patients with breast	47

Breast cancer	breast tissues	of women P=130		Escherichia coli are observed.	cancer had mean levels of IL-19 that were considerably lower than those with benign breast lesions.	
	Breast tissues	33 to 84years of women P=33	16s rRNA Sequencing and processed with hybrid denovo pipeline. Multilinear regression and Permanova	Staphylococcus and firmicutes were detected.	Future breast cancer risk is increased by changes to the microbiota and the stroma in the breast.	[48]
	Fecal sample	30 to 60 years of women P=62 C=71	Metagenomic DNA seq by Illumina Hi Seq*10 platform, SPSS,PERMANOVA	*Escherichia coli, Enterococcus gallinarium, Citrobacter koseri, Erwinia amylovora,* and *Shewanella putrefaciens* have all been identified.	Dysbiosis in the gut microbiota is hazardous, as it has been linked to the development of postmenopausal breast cancer.	[49]
Leukemia	Oral mucosa	3 months to 276 months P=71	PCR followed by DNA seq method and other culture tests.	Herpes simplex virus and candida were detected	HSV and candida are unequivocallyconnected to a raisedrisk of mucositis in children and grown-ups with acute lymphoblastic leukemia.	[50]
	Oral (buccal swab)	23 to 84 years P=39	16s rRNA, illumine Miseq platform, Kruskal-wallis test, Mann-whitney test, Spiec easi	Candida, Alternaria, cladosporium, fusarium were observed.	Invasive mold infections in patients are primarily caused by Aspergillus. Chemotherapy results in modifications to the oral microbiota.	[34]
	Supragingival plaque was collected from the mesial surfaces of teeth.	Mean value is 7 P=13 C=12	Qi Aamp DNA micro kit, 16S rRNA , pyrosequencing,	Phylum Fusobacterium and fermicutes were abundant	Growing opportunistic microorganisms could be a major risk factor for systemic infections in leukemia patients.	[35]
	Stool sample	N=48	16S rRNA and metagenomic shotgun sequencing	Bifidobacterium, bacteriodes, blautia, longicatena are present	Differences in the intestinal microbiome after anti-CD-19 CAR-T-cell therapy for B-cell malignancy were connected to clinical outcomes.	[36]
Melanoma	Stool sample	Mean age 41 to 66 years P=20 C=16	16 rRNA, greedy denovo OTU picking, PERMANOVA, ANOSIM,	*Anaerobacerium chartisolvens, Prevotella copri, Bacteriodes ovatus, Victivallis vadensis* were observed	Regression of melanoma is strongly correlated with gut fungus patterns.	[39]
	Skin and stool samples	6,8,10 and 12 weeks of piglets P=24 C=10	Qi Aamp Power Fecal DNA kit, DNeasy Power Biofilm kit, 16s rRNA gene, Kruskal-Wallis test, visualized using R studio	Fusobacterium and Bacteroides were detected in both melanoma tissue and the fecal microbiome.	Between melanoma progression piglets and healthy piglets, differences in bacterial composition, diversity, and metabolic pathways were seen.	[42]

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	Stool samples	12 week old female mice	Qi Aamp DNA stool mini kit, 16sS rRNA, In vivo imaging system, µCT based analysis, Kaede mouse cell photo conversion, real time reverse transcriptase PCR,	Antibiotic-induced gut microbiota reduction accelerates tumour growth and inhibits NK cell and T cell migration to the tumor-bearing bone.	The intestine microbiome moderates the development of melanoma bone injuries in mice by advancing the production of intestinenaturalkiller cells and Th1 cells and upgrading their relocation to the tumor-bearing bones.	[51]

CONCLUSION

Microbiomes are a dual-edged weapon in cancer treatment.This review discusses the dysbiosis of the microbiome in several types of cancer, demonstrated multiple ways that bacteria might influence tumor growth, and investigated the relevance of the microbiome in immunotherapy. In addition to disrupting the host defense system, cancer is caused by the production of tumor proteins as a consequence of metabolism.Microbiome dysbiosis unequivocally plays a critical role in cancer formation, progression, treatment, and predisposition. The microbiome is a definitive biomarker for predicting targeted treatment efficacy.Multimodality therapy is being investigated to overcome immunological resistance and the side effects of conventional medicine. Because of its high affinity and peculiar peptide ligands for solid and haematologicaltumour therapy, phage display technology is a powerful nanotechnology with various applications. Thus, phage display technology contributes to the resolution of several issues by providing a single platform for the transfer of desirable genetic agents, which inhibits cancer growth and progression while also promoting resistance development. Understanding the cellular and organism-level mechanisms of the microbiome will assist in enhancing the quality of life in the future by preventing numerous diseases.

Abbreviations:
A2AR: Adenosine A_{2A} receptor
AC: Adenocarcinoma
ALL: Acute lymphoblastic leukaemia
cAMP: Cyclic adenosine monophosphate
CAR-T: Chimeric antigen receptor
CD-8: Cluster of differentiation-8
ERK: Extracellular signal regulated kinase
FMT: Fecal microbiota transplantation
HSV: Herpes simplex virus
IFN: Interferon
IL- Interleukin
MEK: Mitogen activated ERK kinase
NA: Not available
NK: Natural killer cells
NSCLC: Non-small cell Lung Cancer
OUT: Onal taxanomic units
PC: Pancreatic cancer
PCR: Polymerase chain reaction
PD-1: Programmed cell death protein-1
PKA: Protein Kinase A
RAF: Rapidly accelerated fribrosarcoma
RAS: Rat sarcoma Virus
RIC: Remission induction chemotherapy
SCC: Squamous cell carcinoma
SPSS: Statistical package for the social sciences
STAT: Signal Transducer and activator
TGF: Transforming growth factor
Th1: Type 1 T helper cells

Declarations:
Authors' contributions:KS did the literature search and prepared a first manuscript. BV, SV and CGP analysed the data. DVLand DVRreviewed the manuscript and made a necessary corrections. All authorsread and approved the final manuscript.

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