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Review Article

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THE UPSURGE IN THE FIELD OF PHAGE -BACTERIA- EUKARYOTIC ASSOCIATION BESIDES THEIR IMPACT ON HUMAN HEALTH ALONG WITH DISEASE- THERAPEUTIC IMPLICATIONS WITH ESCALATING ANTIBIOTICS RESISTANCE-A MINIREVIEW

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ABSTRACT

Having reviewed the role of gu**t** microbiota(GM)in human obesity, type 2 Diabetes mellitus(T2DM), Non alcoholic fatty liver disease(NAFLD), metabolic syndrome(MetS) and further extension to development of neuropsychiatric diseases(NPD), here we did a minireview regarding gut virome and impact of triad symbiosis. An escalating research divulges the individuality along with in general astonishing modes by which bacteriophages that are viruses that have become specialized with regards to bacteria, possess the capacity of impacting human health along with diseased stages. This might take place directly by influencing their host bacterial ecology via top down pressure or through greater indirect means inclusive of impacting human body metabolism or immune system. These crosstalk of microbes possess the capacity of impacting health along with disease by affecting the local milieu or via body's distant organs/ systems. Thus we carried out a minireview with the utilization of using the pubmed, Web of Science, Medline, Embase, Cochrane reviews, and Google Scholar, Search engine with the MeSH Terms; Gut Microbiota(GM); bacteriophage; human health; immune system; antibiotics resistance; triad symbiosis; genetic engineering from 2010 onwards till date in 2022 we found a total of 6000 articles out of which we selected 51 articles for this minireview. Thus we describe the present insight with regards to impacting human health with regards to tripartite symbiosis with the bacterial as well as human hosts. Furthermore, the clinical applications in this era of antibiotics resistance as well as clinical trials in lung infections is detailed.

KEYWORDS: Bacteriophages; Gut Microbiome; metabolome; antibiotics resistance; triad symbiosis.

1. INTRODUCTION

The human body has a symbiotic association with a wide range of microorganisms which are basically located on its surface, however exist right through the body. These microbes are comprised of symbiotic bacteria that generate themaximum components of the microbiome with the bacterial viruses usually labelled as bacteriophages/phages for simplicity. It is significant to emphasize that such microbes do not reside in the body alone. Rather they crosstalk with the host along with microbial communities develop inherent along with linked symbiosis.

Escalating clarification is being revealed recently with greater publications that such bacteria possess a key part in human health besides across separate pathological events. At the time of healthy stages, bacterial species might possess a cooperation with its human host in a pleiotropic manner by i)aiding in the host metabolism, immune cell working, besides barrier protection

conferring amongst a wide variety of other key functions. Nevertheless, on breakdown of this refined microbial balance this system can swing towards a diseased stage usually known as dysbiosis. Gut dysbiosis is escalatingly correlated with a broad spectrum of Intestinal pathologies with enhanced validation illustrating its association with colonic microbiota, their metabolic end products along with human immune system.[1]

Enhancing proof illustrates that phages, their bacterial hosts along with human hosts generate a key ternary crosstalk which can regulate health as well as disease stages. This review is meant for emphasis of recent publications regarding variable astonishing manners by which phages can impact their bacterial along with human hosts, with robust concentration on trilateral modes. These crosstalk might takes place directly through phage acting as carnivores of bacterial bionomic environment or through indirect manners like an impact on metabolism as well as immune system. Acquisition of insight regarding these modes along with the method by which they function in separate parts of the body would be essential for future evaluation with utilization of microbial therapies for health therapies.

2.1 Human Gut Phages

The gut microbiome possesses considerably significant part regarding modulation of human health. This gets guided by a variety of microbial community whose basic function is to contribute in human digestion, however is **i**ntricately implicated in the generation of variety of metabolites, avoidance of Infection, besides maturation of immune system along with several other parts. The next step in gu**t** microbiome is deciphering its viral components, mainly bacteriophages.[2]

The generation of Human gut virome is **i**ntricately correlated with our human generation along with aging which shifts on various successions of viral diversification. To assesshow the gut virome formation takes place Liang etal.[3], observedthat infant's meconium illustrated occasional to nil viral particles, however only at one mth of postpartum period their was an appreciable enhancement of viral load equivalent to 10^9 viruses/g of feces. The query arising from this is the source of these viruses. On combination of in vitro along with Bioinformatic methods Liang etal.[3], illustrated that early colonizing bacterial species in the infant's gut generated a mainly lysogenic(temperate) phages community possessing greater viral heterogeneity. Subsequent to infancy, a noticeable limitation of the enrichment in addition to escalated colonization of eukaryotic viruses (although at much lesser quantities.[3] Mathieu et al.[4] in a similar strategy, accumulated 648 fecal samples from 1year old child cohort, following which 900 *Escherichia Coli* (E.Coli) strains that were utilized for contrasting the Infective potential of temperate as well as lytic(virulent) coliphages possessing greater quantities that were isolated spontaneously liberated functional temperate phages, with these phages having a minute host range, with just 8% of phages illustrating breakdown of the evaluated strains.[4] Relatively, under $1/4^{th}$ of the fecal virome samples possessed virulent coliphages, despite the ones observed illustrated a significantly greater host range with breakdown of 68% of the E. Coli that were isolated. Hence these studies illustrated that the infant's human gut virome gets formed by the early bacterial colonization which anchor temperate phages with limited host range[3,4], subsequent to which slow along with gradual escalation of viral assortment in the lifespan that follows.

A crucial colonization process is the finding of crAssphages in the human GIT.[5] These phages reflect a substantial along with omnipresent family of phages, observed in over 50% of persons with a worldwide distribution, with the capacity of Infecting the symbiotic Bacteroidetes present in the GIT along with in certain conditions might comprise greater than 90% of a person's gut virome.[6,7] In view of crAssphages being virulent phages is correlated with a swing to a greater dominance of a virulent phage community.[6,8] Recently in one of the maximum exhaustive gut microbiome assessment, conducted by Shikoporov etal.[9], in 2019till date where they conducted longitudinal metagenomic sequencing of the microbiome along with virome in case of 10 healthy adults in a span of in one year. Their observation was substantial divergence with amongst 10^8 as well as 10^{10} viral genome copies/g of feces along with greater than 39,000 viral genomes picked up overall.[9] Dominance of adult gut virome by minute quantities ofconsiderably personalized viruses, mainly comprising of virulent crAss-like along with Microviridae phages which were considerably stable at the time of one year span. Remaining virome possess much lesser stability, that was inclusive of phages having lesser abundance, phages which Infected temporary microbiota members along with other diet correlated viruses. Overall, the human adult gut virome illustrated escalated enrichment of viruses with age, with virulent crAss-like phages developing greater footing in latter years with a milieu of remarkably divergent along with mainly transient phages.

Whereas our insight regarding the progression, diversification along with human adult gut virome life spanhas escalated considerably, still plenty of lacunae are still found concerning the crosstalk amongst these viral communities studies along with theirbacterial as well as human hosts. However for gaining insight, requirement exists for possessing the capacity of estimating them. Apparently this might be a simple job in view of the presence of great quantities of phages in the human GIT that might be greater than 10^{12} particles, the basic hurdle presents itself at the time of an attempt at Identification of the viral sequences against a complicated mixture of microbial community milieu along with the absence of viral markers which are universal.[8] Significant propagation regarding these

concerns have been made by 2 studies via construction of 2 complementary gu**t** virome databases. The Gu**t** Virome Database(GVD)from publications of greater than 33000 individual viral population that were collected by Gregory etal.[8], from 32metagenomic that were inclusive of 2000 personsfrom 16 countries in a complementary strategy. Carmailo, Guerrero etal.21[10], collated the GVD comprising of equivalent to 142,00 non dispensable viral genomes which were extracted from metagenomes along with cultured bacteria isolated. Noticeably, the GVD inclusive of greater than 40,000 total along with good quality viral genomes with a mean genome length of equivalent to 47kb in contrast to equivalent to11kb mean genome length documented in GVD. Both the databases displayed considerably unique virome dynamics which were **i**ntricately correlated with bacterial host distinctiveness along with lifestyles that human beings adapt. A definitive separation of gut viromes was observed in case of urban vis a vis rural types of lifestyles adopted. Furthermore, non Western subjects canonically possessed greater distinctiveness contrasted with their Western analogues.[8,10] Nevertheless, it is necessary to observe a robust association amongst a person's virome along with their microbiome, which pointed to viral variations picked up were with probably guided by gut bacterial hosts. It still has to be ascertained till what degree phages actually determine the gu**t** microbiome vis a vis only representing the present gu**t** heterogeneity[11] with the truth apparently existent somewhere in between.

2.2 Utilization of phages in the form of Anti Microbial Agents

The part of phages along with their probability of impacting different diseases right through body is now clearly realized.[12] Nevertheless, the complex milieu of gut has invoked queries with regards to the efficacy of the canonical phages treatment strategies implicating utilization of a single or cocktail of phages with the basic idea of targeting along with removing any enteric pathogen.

A paradigm -inflammatory bowel disease (IBD) IS strains Crohn's disease (CD), which represents a chronic along with relapsing transmural inflammation involving the gut mucosal layers.[13] Despite, the lack of information regarding the exact etiology of CD, inflammatory microbiome, besides virome constitutents have been correlated with the initiation of symptoms, Clooneyetal.[14], conducted a recent study where exhaustive virome assessment whose publications had been done regarding healthy along with IBD datasets of patients which displayed an escalated enrichment of temperate phages in CD patients. Whereas healthy individuals viromes had a dominance of virulent core that is in agreement with the present insight regarding the succession of gut virome with alterations along with dynamics in adults[9], while this virulent core virome was missing in IBD patients whose replacement was subjects particular switch to a temperate virome.[14] Environment stimulators that were correlated with inflamed gut were posited to result in induction of temperate phages which in turn caused a decreased gut bacterial assortment in view of the activation of lytic phage life cycle along with escalated the comparative enrichment of temperate phage virions in IBD patients small intestinal tract. Considering the bacterial colonization,a particular pathogen group that was observed to be aberrantly common on the ileal mucosa of CD patients were adherently invasive *Escherichia Coli*(AIEC)[15,16] Gaitier et al.[15], in a targeted strategy in 2017 for reducing AIEC in the GIT, observed that delivery of 3 virulent phages that were targeting AIEC to transgenic mice which expressed the human receptor for AIEC resulted in significant disease in fecal along with adherent flora of the small intestinal sections in an antibiotics stimulated model of dysbiosis.Of significance is the fact that only one dose of the cocktail of 3 virulent phages was enough for avoidanceof propagation of the symptoms of intestinal Colitis at the time of 2 wks duration.[15]

This phages targeted elimination of the pathogenic bacteria in the gut was not limited to Gastrointestinal Tract(GIT) diseases along with their utilization is feasible for the treatment of) diseases that are beyond GIT. Duan etal.[17], recently illustrated **a** positive association with non alcoholic steatohepapititis besides colonization of the GIT with *Enterococcus fecalis* strains which generate a substance cytolysin.[reviewed in ref no-18](figure1). Following generation of cytolysin in the gut its translocation to the liver resulted in escalated liver damage along with hepat**o**cyte demise resulting in reduction of liver function as well as enhanced mortality. With the utilization of a humanised mouse model, these authors delivered the phages which targeted the cytolytic *E. Fecalis* strains leading to reduction of gut colonization subsequent to which decreased generation of cytolysin along with ameliorated ethanol stimulated liver injury, steatohepapititis along with inflammation.[17] Noticeably, phages appropriately targeting GIT pathogens led to amelioration of tissue damage outside the GIT, illustrating that phage preying on bacteria in the gut might have a substantial influence influence on the mammalian host.

The targeted elimination of particular bacterial species. strains from the GIT has been believed for long to be a key hallmark in biological treatment options .Hsu, etal.[19], recently evaluated the utilization of lyticphage targeting bacterial hosts within a individual specific10 member gut bacterial cartel amongst a humanized mouse model. Astonishingly, preying by phages besides decreasing target bacterial hosts comparative enrichment amongst the gut they further resulted in transfer in the non target bacteria via inter bacterial crosstalk leading to flowering along with attenuation of certain species[19] These alterations modulated by cascading phages in the microbiome further modulated the gut metabolome with decreased generation of neurotransmitters(tryptamine along with tyramine) as well as escalated generated some

aminoacids(serine as well as threonine). Despite, the outcomes obtained of phage modulated manipulation of gut metabolites are still in early stage with this study displaying that preying by phages of their target species in the GIT is correlated with swings in the broader microbial community associated with the generation of particular metabolic end products(figure1).[19] It still has to be found out how much this would have an impact on application to greater than specific10 member gut bacterial community.

2.3 Phage Nanotechnologies, enzymes along with Amelioration of Virulence

Since the phages possess individualized properties in particular it has aided in the generationof phage-driven nanotechnologies regarding appropriate delivery of substances along with agents possessing a wide extent of therapeutic implications. With the utilization of this strategy Zheng et al,[20], generated a phage-driven, biotic abiotic hybrid nanosubstance whose target was the pro tumoral bacterium *Fusobacterium nucleatum* that aided in appropriate delivery of chemotherapy agents against colorectal cancer(CRC). By separation of a phage which targeted F. *nucleatum* Zheng et al.[20], utilized azide manipulations to covalently associate dextran nanoparticles loaded with a 1st line anticancerous agent with the phage capsid. On delivery, these manipulated phage possessed the capacity of targeting along with removing the intra tumoral *Fusobacterium nucleatum* along with the event appropriately delivered the anticancerous agent to the CRC tumors, hence decreasingthe inimical actions of the common chemotherapy.[20] Yangetal.[21], displayed the utilization of a recombinant phage obtained protein separated from the cell wall binding domainof phage lysin Ply V12 known as V12CBD,for ameliorating the virulent methicillin resistant *Staphylococcus aureus*[MRSA] along with escalated the immune reaction in a mouse model. Subsequent to binding to MRSA,the recombinant V12CBD protein resulted in downregulation of numerous virulence factors, following which it caused decreased MRSA adhesion along with invasion of epithelial cells.[21] Of greater significance V12CBD possessed the capacity of directly activating macrophages via the nuclear factor κB(NF κB) pathway, resulting in escalated macrophage phagocytosis of MRSA as well as decreased inflammatory damage in organs amongst a mouse model of sepsis.[21] Future observations will yield more understanding regarding the diversity of modes by which phages along with their obtained products can impact the bacterial host however with their mammalian host via direct as well as indirect modes.

A well appreciated restriction of phage modulated elimination of bacterial species from the body is the generation of bacterial phage resistance which is unavoidable. Once phage preying takes place, the bacterial hosts are usually made to bargain amongst acquisition of resistance against the lytic phage preying along with fitness expenditure correlated with the sustenance of resistance. Like phage preying of Listeria Monocytogenes Servovar 4b, that is a significant intracellular pathogen needing galactosylated teichoic acids correlated with its cell wall for starting the infection as documented by Sumrali et al.[22] The resistance regarding this phage got generated in view of the elimination of galactosylated teichoic acids that were indirect requirement for the invasion of the host cells, hence ameliorating the pathogen. Another example cited by GordilloAltamirano etal.[23], displayed that robust pathogen *Actinobacterium baumanni* were observed to modulate infection through the bacterial capsule.[23] The phages which were resistant isolates possess the aberrant capsule generation which resulted in the repeat sensitization tohuman complement, βlactam antibiotics, besides alternate phages along with those mutants that had deficiency of capsule were observed to possess lesser fitness in a murine model of sepsis. Whereas these adjustments occur usually secondary to loss of function mutations in phage receptors, they might be modulated by a spectrum of other modes, inclusive of epigenetics. The GIT pathogen *Salmonella enterica* encodes an opv AB operon, that goes through phase differences for generating 2 kinds of subpopulations opv AB^{ON} along with opv AB^{OFF}.[24] The population of opv AB^{OFF} is virulent, however sensitive to phages which utilize O Antigen in the form of receptor, while opv AB^{ON} subpopulation is non virulent, however phage resistant. In the existence of phages which make utilization of O Antigen in the form of receptor, just the survival of non virulent subpopulations occurred.[24] Nevertheless, the phase differences aided in the fast reverting of the virulent opv AB^{OFF} subpopulation the moment there was elimination of phage pressure, thus provision of just a temporary fitness expenditure. In provision of a lysogenic MRSA strain, Li etal.[25], contrasted homozygous MRSA strains from continued endovascular infection with or without clinically obtained prophage, illustrating that the strains which nurtured the prophage were correlated with continued infection.[25] The prophage possessing strains manifested the phenotypes correlated with continued infection, inclusive of sooner activation of global gene controllers, greater purine biogeneration, greater growth factors, lesser proneness to vancomycin, robust haemolysis along with biofilm generation. Hence the resulting lysogenized strains illustrated no clinical reaction to vancomycin therapy along withpossessed significantly greater bacterial densities in all the targeted tissue in an endocarditis model.[l25] Lastly Secor etal.[26], observed that the extracellular matrix[ECM] generated by *Pseudomonas aeruginosa* which fostered Pf prophages possessed the capacity of generating liquid crystals matrix antimicrobial agents through entropic crosstalk amongst biofilm polymers along with the filamentous Pf phages. Escalation of biofilm viscosity that resulted in enhanced adhesion tolerance to devitalization as well as antibiotics was caused by these long negatively charged filamentous virions.[26] Amongst the lung milieu Pf phages aided in

bacterial adhesion to the lung mucus that as a sequelae resulted in greater spread of P. *aeruginosa* bacterial host across the lung milieu along with facilitating chronic airway infections that were in particular clear in cases of cystic fibrosis (CF).[27] Furthermore, Tarafdar etal.[28], illustrated that the phage liquid crystalline biofilms generated by Pf phages matrix, besides encapsulating the P. *aeruginosa* bacterial host, aided in provision of enhanced resistance to a wide spectrum of antibiotics.[28] By getting greater insight in the modes of phage infectiveness, the way their bacterial hosts react to phage pressure, along with their crosstalk amongst the mammalian hosts, we would possess greater chances of generating as well as applications of phages dependent treatment.

3.1 Phages along with Mammalian Immune System

Whereas phages are non canonical pathogens, they possess the capacity of bypassing mammalian immune system[29,30,31] Phage crosstalk with the mammalian immune system can take place indirectly via prokaryotic intermediates or by direct means by internalization along with the receptor recalling by mammalian cells. The mammalian innate immune system possess the broad range of pathogen recognition receptors(PRR) possessing the capacity of recalling the preserved molecular epitopes observed in bacteria along with the viruses. Of significance, microbially obtained nucleic acids with unique architecture get recalled in the form of foreign or alien along with have the capacity of induction of robust immune reactions. Of significance microbially obtained nucleic acids with unique architecture get recalled in the form of foreign or alien along with have the capacity of induction of epitopes observed robust immune reactions.[32,33] Robust proof regarding capacity of phages of modulating innate immune reactions was recently illustrated by Sweere et al.[34], with the utilization of filamentous P. *aeruginosa* Pf phages. Pf represents a filamentous phage possessing ss DNA genome which generates liquid crystalline matrix which encases its P. *aeruginosa* bacterial host facilitating biofilms generation along with chronic airway infections.[26,27] Extrapolating these observations illustrated that wounds which had been infected by Pf positive P. *aeruginosas* strains possessed greater correlation with chronic wounds which fail to get repaired in contrast to strains not possessing Pf phages.[34] With the utilization of human along with murine leukocytes Sweere et al.[34], illustrated that endocytosis of Pf phages took place resulting in generation of phage RNA, that in turn caused the activation of PRR toll like receptor 3 (TLR3). Subsequent to this activation of TRIFbased type1 interferon formation that was followed by hampering of Tumor necrosis factor alpha(TNFα) formation in the wounds milieu(figure2A). Hence amelioration of phagocytosis following clearanceof Pf phages P. *aeruginosa* from the wounds milieu once TNFα) formation was hampered, resulting in continued P. *aeruginosa* along with chronic wound infections.[34] Akin to that subsequently Jahnetal.[35], evaluated the existence of ankyrin repeat domains(ARD) amongst phage populations correlated with marine sponges**,** however further observed amongst phage populations in the human body inclusive of the oral cavity along with gut. On infection of their hosts bacterial cells possessing ankyrin containing phages stimulated the liberation of ANK proteins that escalated bacterial survival at the time of coexistence of murine macrophages[35] Incubating macrophages with ankyrin generating *E.coli* cells resulted in the decrease of proinflammatory cytokines TNFα,Cxcl1, along withIfn1 that following that caused reduction of phagocytosis of the bacterial cells. To summarize, viral innate immune reactions were changed secondary to a symbiotic association amongst phages along with their bacterial hosts resulting in escalated continuation of bacteria along with phages in the body.

The existence of whole phage along with their constituents that might be inclusive of genome DNA /RNA, proteinaceous capsids along with remaining bacterial constituents like lipopolysaccharides (LPS) all possess the capacity of directly stimulating the mammalian immune reactions. Gogokhia etal.[36], recently illustrated in a study that started with the assessment with the utilization of a phage cocktail regarding the targeted elimination of the intestinal pathogen AIEC that is correlated with colorectal Cancer(CRC). Continued oral delivery of the phage cocktail to mice caused a decrease in AIEC from the intestine, downregulation of genes correlated with tumor growth metastasis along with protection conferred from bacteria aggravated CRC.[36] However regarding assessment of gene expression outcomes, upregulation of a huge group of immune pathways was observed in the group which received phage treatment vis a vis control mice groups. Moreover, it was illustrated that the escalated enrichment of phage in the GIT resulted in the generation of IFN-γ via a TLR-9 pathway[36] probably through dendritic cell(DC)sampling of intestinal phages, unmethylated phages that was later brought to CD4+Tcells(figure2B). Noticeably, it is probable that other IFN-γ activation pathways are feasible.[36] Lastly extrapolating these observations to a murine model of IBD, cocktail of *Caudovirales* phages was administered to wild kind TLR-$9^{-/-}$ along with IFN-$\gamma^{-/-}$ mice along with inflammatory signatures were assessed. Whereas disease robustness deteriorated on phage cocktail delivery in wild kind mice, both the TLR-$9^{-/-}$ along with IFN-$\gamma^{-/-}$ mice received protection conferred from phage escalated colitis along with had decreased inflammatory reaction.[36] These outcomes illustrated the mode regarding theway GIT phages can impact the intestinal immune reaction.

3.2 Mammalian immune system impacts the bacterial along with phage symbionts

Since phages along with their bacteria lhost possess the capacity of impacting the mammalian immune system, the mammalian host's immune reaction possesses the capacity of in turn impacting the bacterial along with

phage symbionts. With the utilization of a murine *Salmonella typhimurum* diarrhoea model Diard etal.[37], illustrated that gut inflammation stimulated the induction of prophages resulting in the escalated lysogenic transformation along with the propagation of enteric disease. *Salmonella typhimurum* genomes in general shield prophages, certain of which encode for genes which are virulent, correlated with escalation of epithelial invasion along with aggravate enteropathy regarding their bacterial hosts. For assessment of the lysogenic transformation dynamics, utilization of 2 *typhimurum* strainswas made;a donor strain possessing the prophage SpoEφ, that encode for a virulence factor along with a non lysogenic recipient strain.[37] Colonizationof the gut occurred equally by both donor as well as recipient strains, however subsequent to coinfection, the frequency of the recipient lysogen escalated gradually; subsequent to 3days postinfection lysogen quantities far exceeded that with the non lysogenic strains in greater than 50% of the animals. In vitro, maximum activation of prophages through the stress stimulated SOS reaction, resulting in escalated induction of SpoEφ along with the escalated lysogenic transformation of prone strains in thegut.[37] This illustrated that the mammalian host's innate immune reaction was a crucial factor that impacts phage bacterial dynamics along with the propagation of disease.

Attempting to avoid gut inflammation along with the propagation of disease, Diard etal.[37], carried out treatment of mice with the utilization of an oral vaccine which effectively conferred protection against tissue invasion by *Salmonella* besides inflammation with out decreasing full *Salmonella typhimurum* luminal quantities. Of importance significant reduction of disease propagation along with lysogenic transformation subsequent to vaccination.[37] This was noticeable since at the time of mammalian host's innate immune reaction was proinflammatory resulting in escalated phages spread along with the propagation of disease, vaccination along with the following IgA modulated adaptive immune reaction illustrated the disease propagation.[37] This approach of phage immunization for disease avoidance was evaluated akin to that by Sweere etal.[34], in their model of wound colonization by Pf phages P. *aeruginosa*. In this situation, immunization of mice was attained with the utilization of a peptide from the main coat protein of Pf phage for formation of humoral immunity with vaccination decreasing the incidence of P. *aeruginosa* wound infection by about 50%.[34] These observation were then extrapolated with the utilization of monoclonal antibodies(mAB) produced against the same Pf phage coat protein followed by applications to the previously colonized wounds which resulted in a considerably significant decreases in P. *aeruginosa* load through escalated phagocytosis. By acquisition of insight regarding the pathogenic part of phages in bacterial disease, it might become possible for formation of greater immunization approaches, that target preserved phage epitopes, hence avoidance of disease propagation.

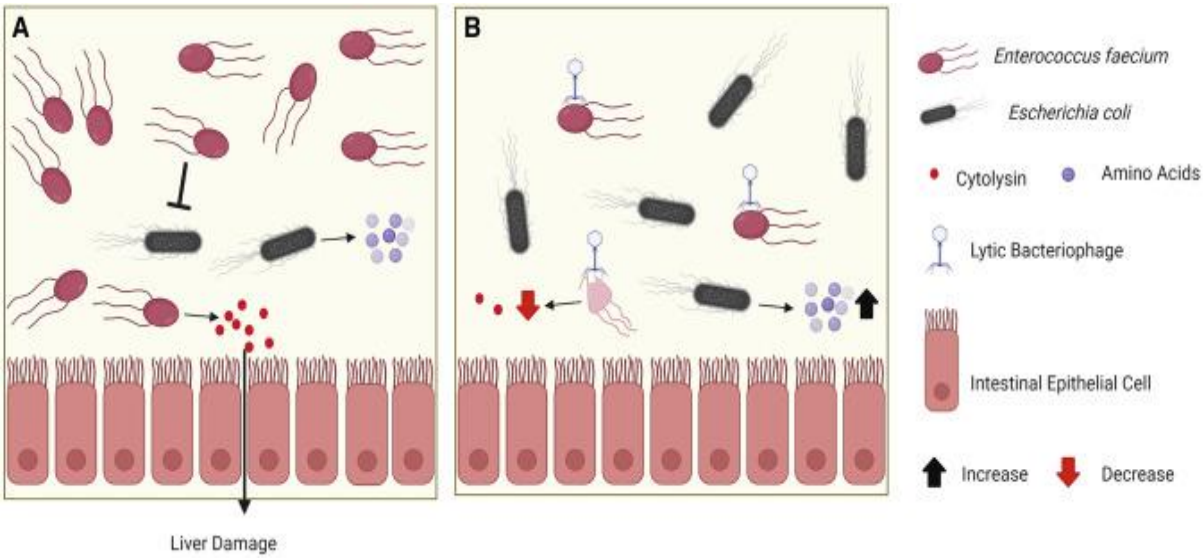
What needs to be emphasized is that the mammalian adaptive immune reaction remains active against gu**t** microbiota(GM) inclusive of phages, with some microbial antigens possessing the capacity **of** stimulating memory Tcells.[38] Moreover memory reactions by IFN-γ liberating CD4+Tcells as well as CD8+Tcells particular for gu**t** microbes are acknowledged to occur occasionally, interact with tumor associated antigens, aiding in anti tumor immune reaction.[39] Recently Fluckiger etal.[40], extrapolated this idea for illustrating that cross reactivity amongst a major histocompatibility complex(MHC) class I-limited antigen as well as an enterococcal phage protein. They observed that the synergistic bacterium *Enterococcus hirae* gave shelter to a prophage which encoded a MHC Class I limited Antigens in the tape measure protein(TMP).[40] Micethat had been colonized by *Enterococcus hirae*, possessing this prophage had the capacity of generating a TMP particular CD8+Tcells reaction on therapy with a chemotherapeutic drug which resulted in induction of E. *hirae* translocation from the gut to the spleen. One dominant epitope amongst phage TMP1 was illustrated to mimic the oncogenic peptidePSMB4. Delivery of the TMP1peptide, directly to DC's or expressed on the surface of *E.coli* was enough in hampering tumor growth metastasis along with escalated the reaction to immuno therapy. Lastly back to the gut microbiota eco system Fluckiger etal.[40], illustrated that the TMP1peptide encoding prophage possessed the capacity of lysogenization of the symbiont microbe *Enterococcu gallinatum* within the gut emphasizing the probability of wide spread of these phages.[40] With the recognition remarkable variety of gut microbiome along with that the gut virome apparently is dominated by few unique but stable phages[8],a probability exists that numerous other microbial possessing the capacity of stimulating an adaptive immune reaction along with impacting human health as well as disease stages.

4. Antibiotics Resistance Tackling

The antimicrobial in addition to therapy effectivenessof bacteriophages is at present restriced mainly in view of fast formation of phage resistance along with incapacity of maximum phages separated of binding along with infecting a wide spectrum of clinical strains. Lenemann etal.[41], described the way improvement regarding treatment via recent advancements along with genetic engineering is feasible. Initially they detailed the strategy of receptor binding proteinsas well as their structural domains that are of relevance get engineered for directing phage specificity besides avoidance of resistance. Furthermore, they provided a summary of the way reprogramming of phages in the form of prokaryotic gene treatment vectors which administer antimicrobial cargo proteins like sequence particular nucleases regarding targeting cells which by definition exist amongst a complicated microbiomes. Lastly they outlined big data besides innovative artificial intelligence guided strategies which might drive the fashioning of enhanced synthetic phages in future[41] (see figure 3).

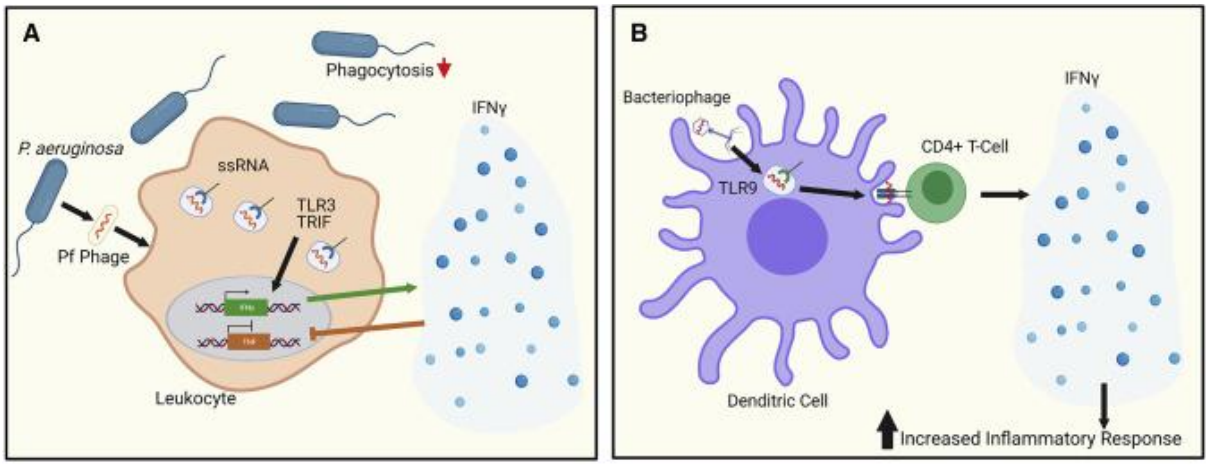
Resistance towards antibiotics is the largest challenge regarding humanhealth worldwide. An escalating incidence of infections whose treatment is becoming considerably difficult inclusive of in certain cases impossible of attaining that goal with a remarkable associated mortality, morbidity along with expenditure involved. Despite phage treatment was initially introduced a century back it was halted then and there with successful antibiotics launch. At present with a significant enhancement of antibiotics resistance resurgence of interest has got invoked in this phage treatment. Gordillo Altamirano along with Barr[42] reviewed the subject with the idea of its utilization in the modern society. The detailed crucial aspects of the crisis we face with the massive antibiotics resistance along with outline the biological as well as evolutionary principles validating the utilization of phages, their crosstalk with immune system along with contrasting antibiotics treatment. With the exhaustive up to date search of clinical trials assessment was done regarding how versatile phage treatment might be. They described the usual in addition to innovative strategies inclusive of combination of phage-antibiotics, phage- obtained enzymes, modes of phage resistance along with phage bioengineering. Moreover, they described the advantages of phage treatment over and above the clinical angle, besides efficacious education, interdiscipline collaboration in addition to cultural along with economic growth as well as novel utilization of social media promoting the phage treatment as an alternative therapy to antibiotics[42] (see fig 4 &5).

Further updates presented in ref no 43 &44.



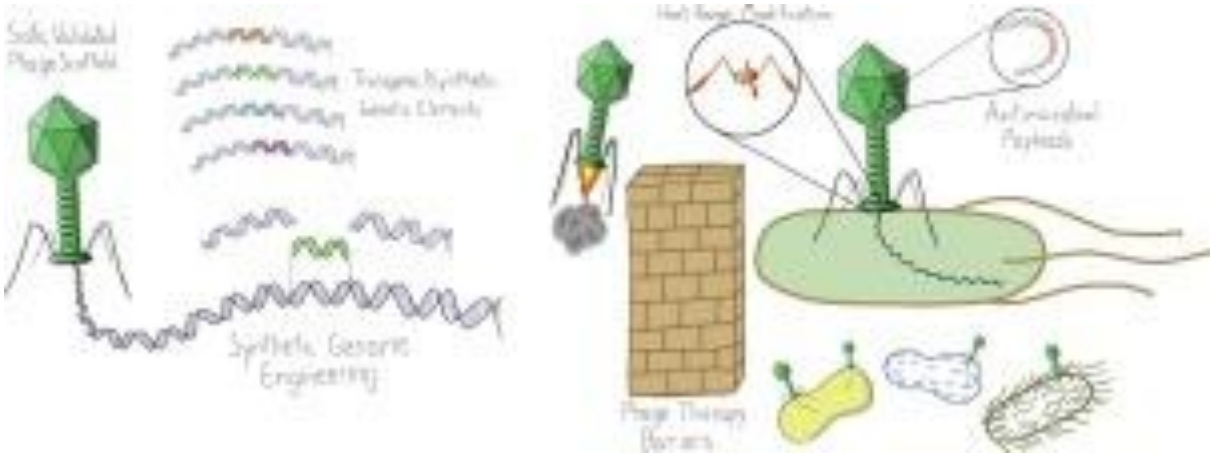
Legend for Figure1.

Courtesy ref no-18-The intestinal microbiota is known to be associated with various health and disease states through theproduction of metabolites and toxins, respectively. Phage predation in the gut has been shown not only to mediate direct antimicrobial effects on their respective bacterial hosts via top-down predation, but also to effect metabolite and toxin production in off-target bacterial hosts via inter-bacterial competition and expansion of niche space (Hsu et al., 2019)

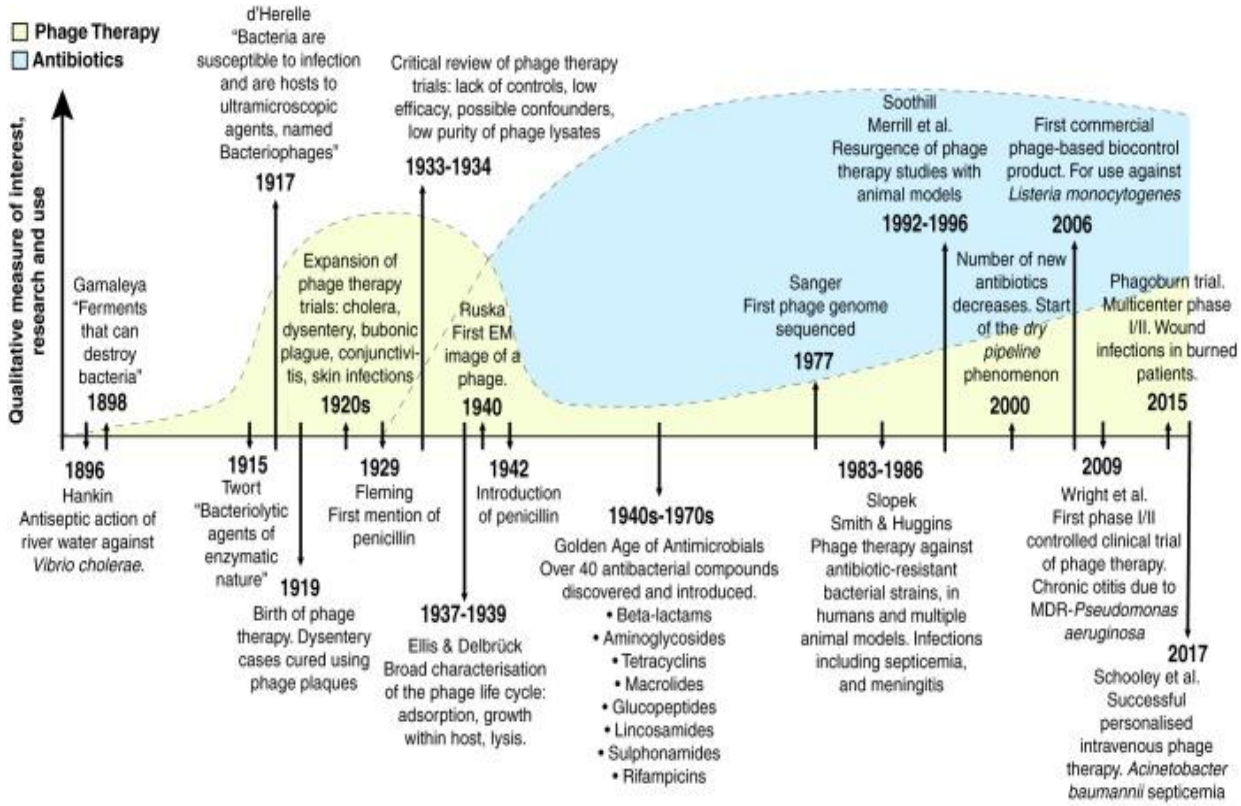


Legend for Figure2: Courtesy ref no-18- phages and their components can direct stimulate the immune system. (A) *Pseudomonas aeruginosa* harboring the lysogenic Pf phage produce the filamentous phage in a wound

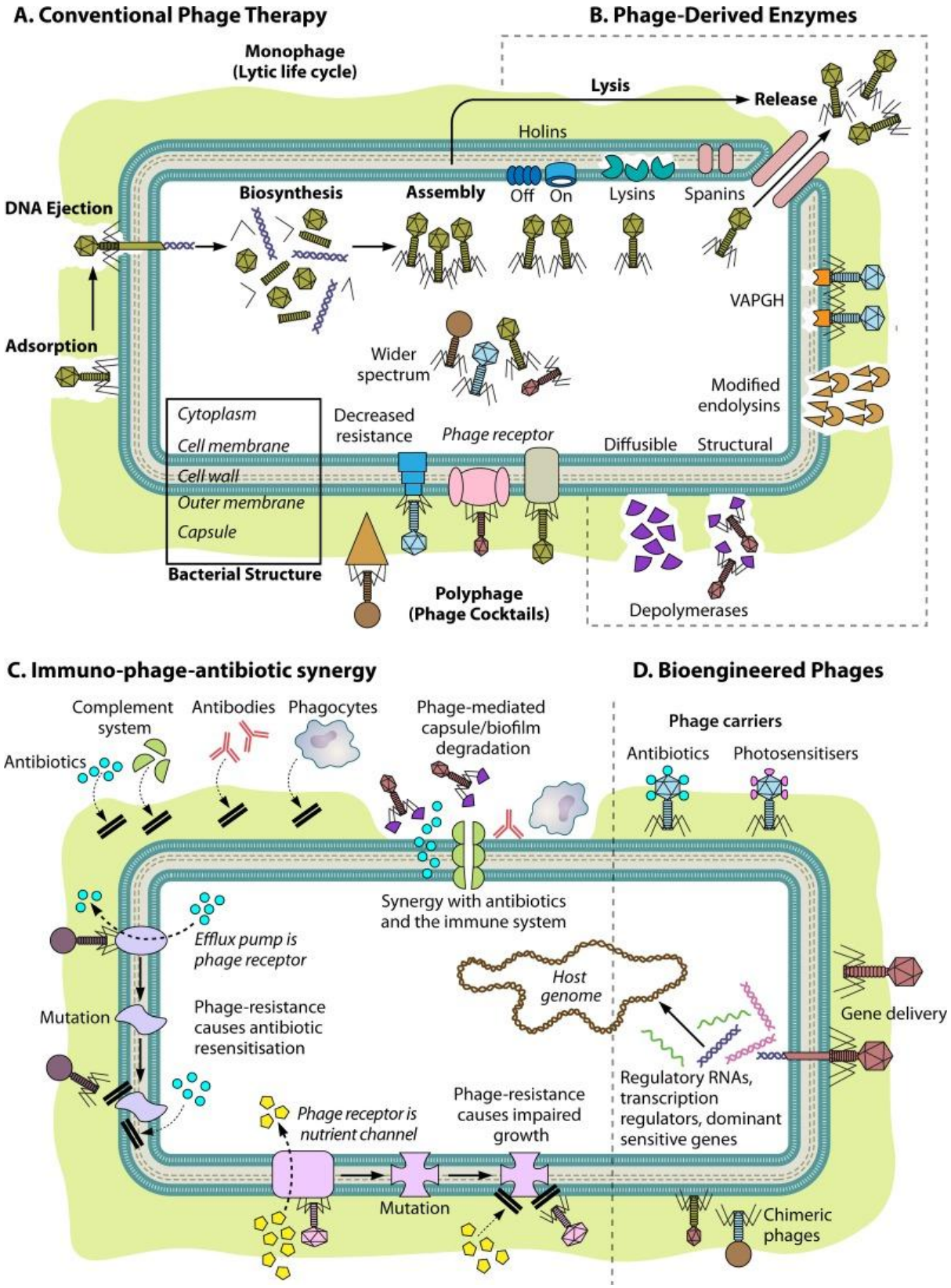
environment. Pf phage is subsequently internalized by leukocytes with phage ssRNA triggering TLR-3 in a TRIF-dependent manner, resulting in the production of type I interferon, which subsequently inhibits TNF production. With reduced TNF in the wound environment, phagocytosis of *P. aeruginosa* is reduced, leading to persistent and chronic wound infections (Sweere et al., 2019)



Legend for Figure3: Courtesy ref no-41-Graphical Abstract.



Legend for Figure 4: Courtesy ref no-42-Timeline of major events in the history of research on phages, phage therapy, and antibiotics. Background curves represent a qualitative measure of the overall interest, research, and use of phage therapy (yellow) and antibiotics (blue), showing how the introduction of antibiotics and the critical review of the early phage therapy studies coincided to bring phage therapy research and development to an almost complete standstill around the 1940s.



Legend for Figure 5: Courtesy ref no-42- Approaches to phage therapy delivery. A schematic representation of a bacterial cell consisting of capsule, outer membrane, cell wall, inner membrane, and cytoplasm is shown. (A) Phage lytic life cycle as the basis for conventional monophage therapy, from adsorption to lysis of the host cell, and polyphage therapy, or use of phage cocktails targeting different receptors on the same host cell, limiting the occurrence of resistance and expanding the therapeutic spectrum. (B) Use of phage-derived enzymes such as depolymerases (to target capsules and biofilm structures) and cell wall-degrading endolysins. Holins, spanins, and virion-associated peptidoglycan hydrolases (VAPGH) are represented as components of the lytic life cycle, without current therapeutic

applications. (C) Mechanisms for synergy between phages, antibiotics, and the immune response include phage-mediated capsule or biofilm degradation, which enables the action of antibiotics, antibodies, the complement system, and phagocytes, and the exploitation of the evolutionary trade-offs of phage resistance, such as antibiotic resensitization and impaired bacterial growth. (D) Bioengineering of phages for therapeutic purposes includes the attachment of antibiotics or photosensitizing agents to phage capsids for targeted release into bacterial cells, delivery of genes to reverse/cancel antibiotic resistance and virulence determinants, and use of chimeric phages. Labels in italic represent bacterial structures.

5. CONCLUSIONS

Having reviewed the role of gu**t** microbiota(GM)in human obesity, type 2 Diabetes mellitus(T2DM), Non alcoholic fatty liver disease(NAFLD),metabolic syndrome(MetS), further extension to development of neuropsychiatric diseases[45-51], here we extended it to study gut virome and its role in normal physiology besides extension to its use in various pathological conditions we have reviewed the resurgence of phage therapy given up a century back. Our insight regarding variety along with usually astonishing ways methods by which phages impact their bacterial along with mammalian host's keeps on escalating once we try to gain greater understanding by in depth assessment of the three party or triad systems. Our present insight of the gut virome is quite similar to that of an infants gut viral variation. Sequencing technologies along with correlated Bioinformatic assessment are moving further at a fast pace which have resulted in significant innovations of crass-like phages in addition to isolation of main gut viral lifestyles. With this information our requirement is of performance of deep Sequencing of the patiens microbiome with wet lab studies of gut phage biology for acquisition of deeper insight of the impact on this eco system. Despite our greater attention towards the antibiotics resistance infections. Nevertheless, caution needs to be exerted regarding not moving over these direct antimicrobial actions along with taking into account the wider impact of phage preying on the microbiome, metabolome as well as mammalian immune system. Lastly the tripartite crosstalk amongst phages, bacteria along with immune system needing multidisciplinary research to unveil. Recent advancements have emphasized the complicated nature of innate as well as adaptive immune reaction to the phages stimulating proinflammatory along with antiinflammatory reactions which aid in health along with disease stages.

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