Identification and Characterization of New Drug Targets Against Gut Pathogens Using Bioinformatics Approach: A Review

Abhishek N L[1], Shreekanth C S[2], Jasmin Rani[3], Virupakshaiah DBM[1*]
[1,2,3] *Research Scholar, Department of Microbiology, Davangere University, Davangere, Karnataka, India – 577007*
[1*] *Professor, Department of Microbiology, Davangere University, Davangere, Karnataka, India – 577007*

***Abstract*—The microbiota is the collective term for the human body consists of vast number of bacteria, fungi, and other microbes that living in the human body. The human gut's ability to absorb, digest, and use nutrients, vitamins, and minerals is greatly influenced by the gut microbiota, which also affects other organ systems and functions. Lifestyle, sex, diet, age, and other genetic factors are all linked to the human gut microbiome, suggesting that the microbiome is shaped by host variables. The molecular and the cellular pathways of microbe–host interactions has been studied, it is increasingly being noticed that cross reactions between the host and its microbes can occur. The ongoing increase in pathogenic bacteria that are extremely resistant to a variety of antibiotics makes it extremely difficult to control pathogenic diseases. Drug research and discovery is a drawn-out and complex process that requires a significant time and financial commitment. In addition to speeding up the process of identifying therapeutic targets, screening, and improving drug candidates, bioinformatics tools and approaches can also make it easier to identify the adverse effects and anticipated drug resistance. The mechanics-based drug discovery and drug reuse, high-throughput data from transcriptomics, proteomics, or whole genomes and metabolomics are crucial. With this scenario, the present review of study aimed to describe and highlight on the bioinformatics approaches in drug research and development with regards to their roles in identification and characterization of new drug targets against gut pathogens.**

***Keywords*— Gut microbiome, Bioinformatics, Drug targets, Druggability, Virtual screening**

I. INTRODUCTION

The term "microbiome" refers to the many number of bacteria, fungus, and other microorganisms that live in the human body.[1] Disseminating the symbiotic interaction between human health, bacteria and disease has become more and more dependent on the significance of the microbiota in the gastrointestinal system. There is number of evidence that the gut microbiota affects many human organ systems and functions and plays a major part in the human gut's absorption, processing, and utilization of nutrients, vitamins, and minerals.[2,3]

The gut microbiome is not only consists of collection of all microorganisms but also their important activity, among them the human stomach serves as a first line of defense and develops alongside the host's innate and adaptive immunity mechanism against enteropathogens, through the activation of non-antigen-specific recognition of receptors, it also aids in the processing of antigens.[4-6] Furthermore, the human gut microbiome is linked to age, sex, diet, lifestyle, and genetic background, suggesting that the microbiome is shaped by host variables.[7,8]

Crosslink between the microbiome and host immune system becoming more well recognized as additional molecular and cellular routes of microbe-host interactions has been discovered.[7,9] In addition to allowing the host to select for microbial traits that influence fitness-related traits like disease resistance, host growth, or reproduction,[10] this crosstalk also enables the host to control or regulate certain aspects of its gut microbiome, which may help maintain intestinal homeostasis,[11] and leads to the evolution of symbiosis.[12] Several symbiotic microbial gut strains and the underlined adverse effects of dysbiosis on the gut organ axis on health are illustrated in Figure 1.

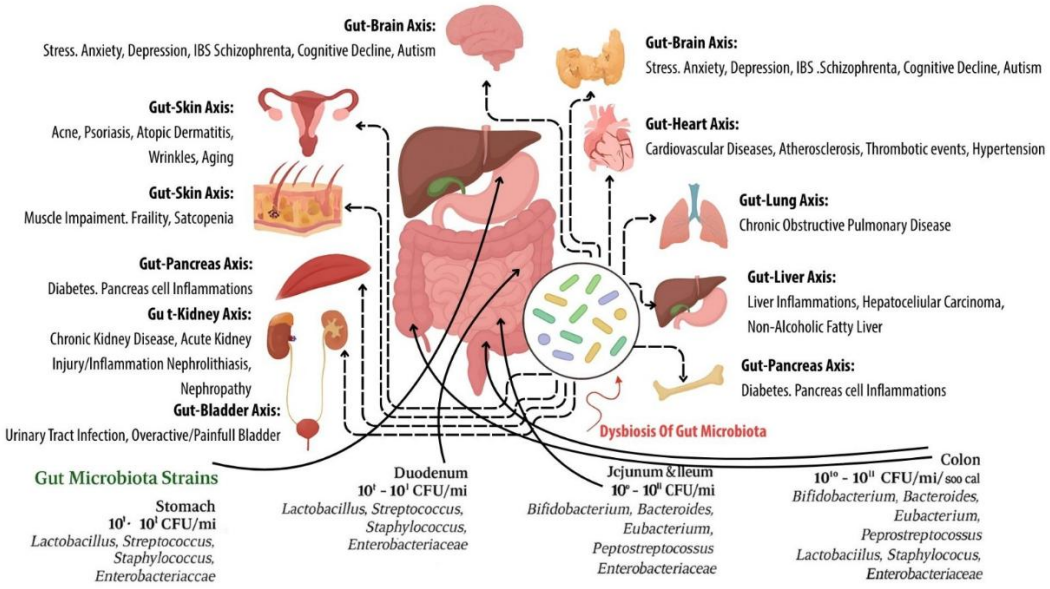

Figure 1. Strains of gut microbes and the detrimental effects of gut microbial dysbiosis on health Afzaal *et al*., (2022)[13]

The ongoing increase in pathogenic bacteria that are extremely resistant to a variety of antibiotics makes it extremely difficult to control pathogenic diseases.[14] The diagnosis of an illness with a well-defined symptom can lower quality of life is the first step in the drug discovery process. According to conventional wisdom, a desirable medicine is a chemical that alleviates symptoms without seriously harming the patient. This chemical would be a basic chemical compound, a complex protein or simple peptides, or a combination of organic molecules.[15]

Finding drug candidates, finding new drugs, and developing lead compounds are all time-consuming, complex processes that require significant financial and human resources. In addition to speeding up the identification of therapeutic targets and the screening and improvement of drug candidates, the use of bioinformatics tools and methodologies can also make it easier to characterize potential adverse effects and evaluate drug resistance. High-throughput data from transcriptomics, metabolomics and proteomics make remarkable contributions to structure-based drug discovery and drug use.[16] With this context, in the present review of literature study we aimed to describe and delineate on the bioinformatics approaches in structure-based drug research and development of lead molecules with regards to their roles in identification and characterization of new drug targets against gut pathogens.

ROLE OF BIOINFORMATICS IN DRUG DISCOVERY

Genomics, proteomics, transcriptomics, population genetics, and molecular phylogenetics are all integrated into the field of bioinformatics.[15]. Biological data, such as gene expression, protein sequence, genome, and biomarker data, constitute the basis of bioinformatics technology. The key elements of bioinformatics technology are the gathering, storing, managing, and analysing of this data, which originates from biological research and experimentation. Number of biological databases have therefore been created to reposition, organize, and distribute life sciences data while incorporating pre-existing resources like technical data and research findings. Table 1 shows some commonly used biological databases that are being used by researchers to retrieve information about biological or bio sciences research to facilitate the development of new drugs and their targets.[16]

Type	Database	Content
Genomics database Gene databases	NCBI NCBI GenBank DDBJ EMBL	Store gene/genome sequences data

Protein sequence database	UniProtKB TrEMBL World-2DPAGE wwPDB	Protein sequences data Translated EMBL data
Genes expression database	NCBI GEO database Array Express	stored gene expression chip/Micro array data
Biomarker database	Metabolomics database BioCyc ChEMBL KEGG	stored biomarker data

Table 1. Commonly used biological database in drug discovery

Drug development has accelerated over the last two decades thanks in large part to bioinformatics software and technologies like high-throughput screening and computational approaches. In addition to offering a crucial approach for the study to produce powerful lead molecules or therapeutic candidates, these techniques are increasingly aiding the screening and development of natural, synthetic, and semi-synthetic compounds. About 36% of recently approved medications are the result of extensive research in the field of natural products and the compounds developed from them.[17]

High throughput molecular sequencing data is often used by computational biologists in drug discovery to compare symptom-carriers (such as cancer cell lines, animal disease models, etc.) with healthy controls (Figure 1). The significant and primary goals of these comparisons are; (i) Linking genetic abnormalities, additional environmental variables that affect gene expression, and epigenetic changes to disease symptoms. (ii) To determine crucial therapeutic targets that can eradicate damaged cells or restore cellular function, (iii) To forecast potential medications that can operate on the target areas to minimize side effects and produce the intended therapeutic impact, and (iv) To lessen the effects on the environment and the possibility of medication resistance.[15]

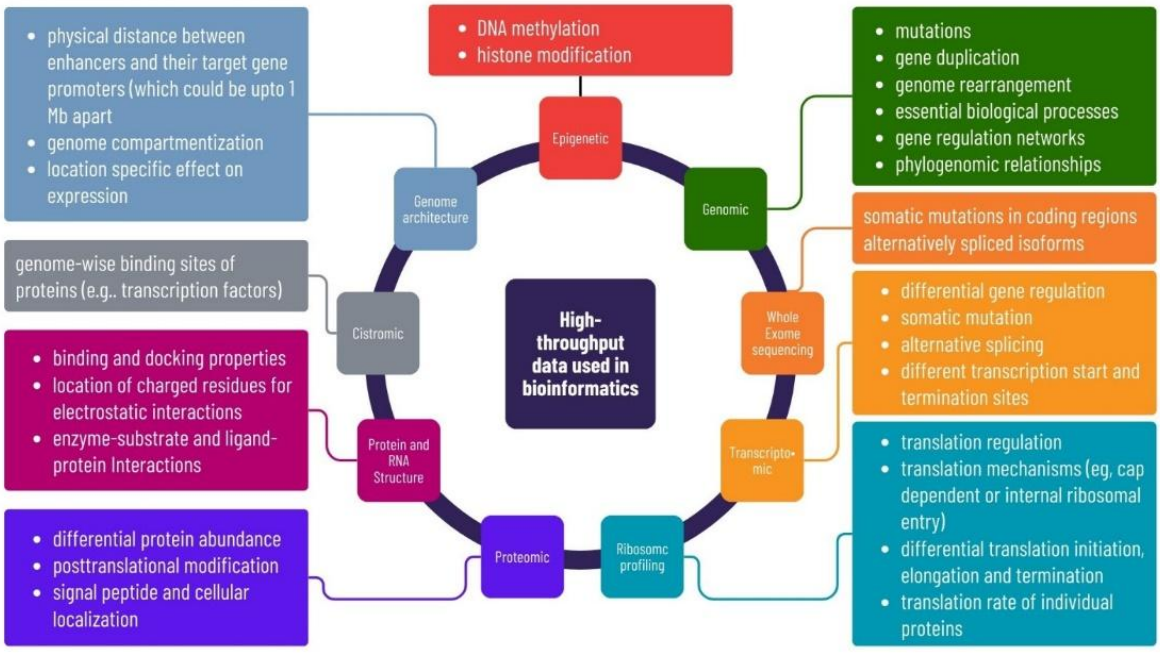

Figure 2. Key information on the main categories of high-throughput data that are pertinent to drug discovery Xia (2017).[15]

ROLE OF GENOME SEQUENCE AND EXOME DATA IN DRUG DISCOVERY

Human diet, age, sex, lifestyle, and genetic background are all linked to the human gut microbiome, suggesting that the microbiome is shaped by host variables.[7,18] Figure 3 presents a conceptually innovative view of the host regulating the composition and activity of its microbiota through epigenetic involvement mechanisms in response to microbial or environmental stimulations.

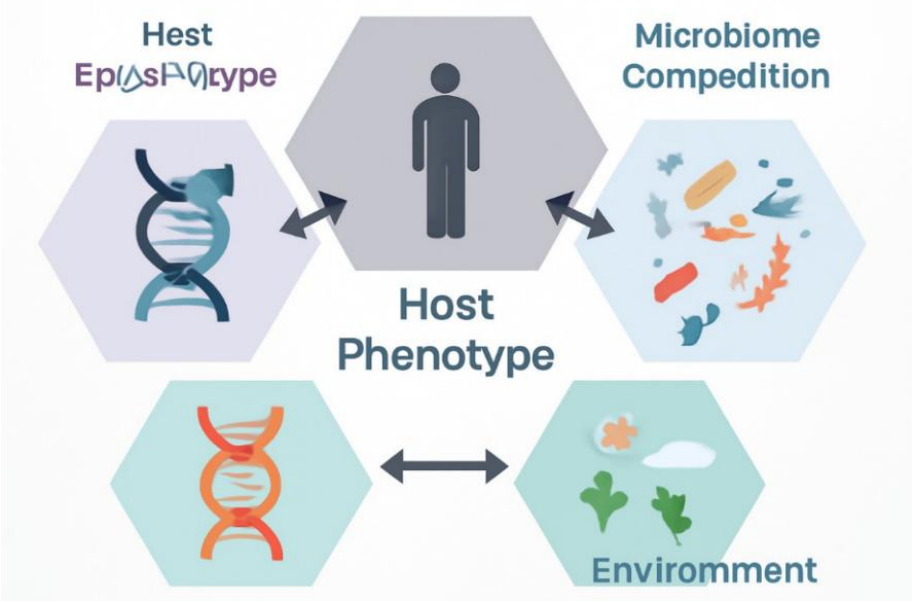

Figure 3. An illustration of the trialogue including the host's genotype, host epigenotype, and gut microbiome Pepke *et al*., (2024).[19] (*Arrows show directions of causality*)

Researchers use a variety of techniques to study host-microbiome interactions in humans, including creating organoids, the gut specimen on a biochip model, employing human cell cultures, or collecting biopsies such as colonoscopy biopsies, gastric surgeries, or colonic surgeries(Figure 4).[20]

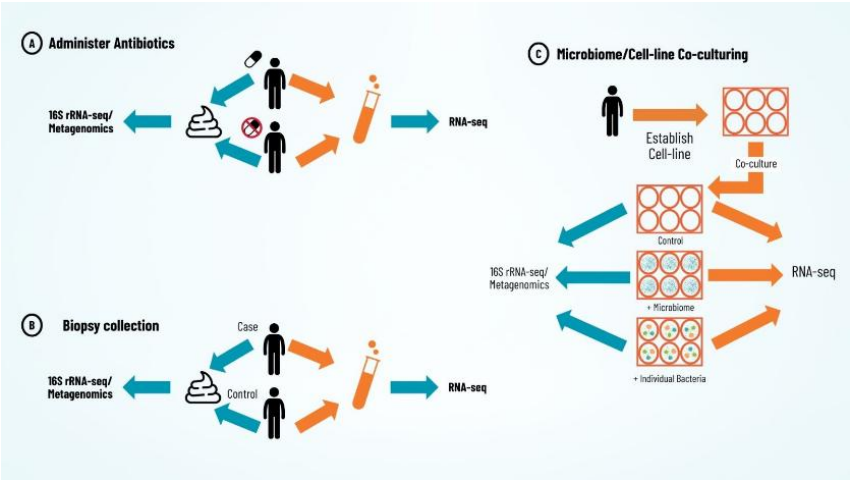

Figure 4. Methods for investigating the connections between human microbiome gene expression Nichols and Davenport., (2021).[21]

IDENTIFICATION OF NEW DRUG TARGETS: APPROACHES

Numerous strategies have been put out for drug targets. locating physiologically active compounds' cellular targets (Figure 4) as follows;

- Affinity-based methods that depend on how proteins and peptides interact with tiny molecules.[22]
- Phenotypic approaches are strategies and tactics used to compare the biological profiles of small

molecules with reference medications that are already well established.[23]

- The genes that cause the resistance displayed by small molecules and small molecule-sensitive clones are found using genetic or genome-based techniques.[24]
- Using chemical structural similarities between the lead molecules of interest, computational methods are used to determine the therapeutic targets.[25,26]

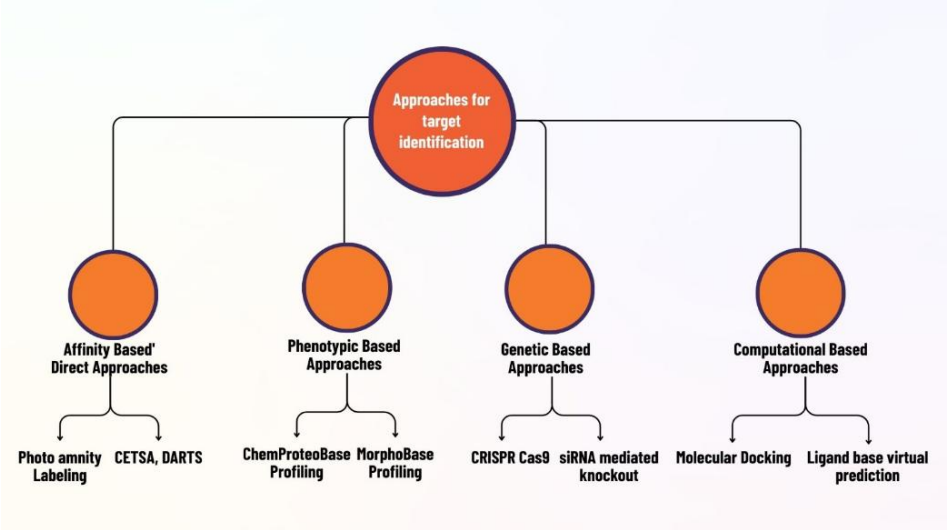

Figure 5. Methods for identifying targets Rasul *et al*., (2022).[27]

All the methods mentioned above, affinity-based methods identify the small molecule targets directly, whilst other methods identify the small molecules indirectly.

DRUGGABILITY DETERMINATION

The capacity of a small-molecule drug to modify a target is known as druggability, and it is a critical factor to determine whether a drug development project moves from "hit" to "specific lead." Predicting the druggability of novel targets is crucial in early drug discovery and development, because only less than 10% of the human genome contains druggable targets, and only half of those are relevant to disease.[28]

Classifying a target with known gene families that have been effectively addressed with medications in the past is often how one determines a target's druggability. However, this strategy has drawbacks because the targets of certain marketed medications are thought to be traditionally non-druggable.[28] There has been news of a novel method for predicting draggability by Cheng *et al*., where they have developed a computational and mathematical model that estimates druggability using structural data about a target's binding site.[29]

The scientists suggested that a target binding site's maximal affinity for a drug-like molecule may be determined by modeling desolvation based on a mathematical model. Desolvation relies on the binding site's surface-area hydrophobicity, which was demonstrated by using recently created computational techniques to the target's ligand-bound crystal structures. For various protein architectures, the calculation's output affinity predicted value can then be translated into a more widely used draggability score (K_d value).[29]

VIRTUAL SCREENING

The most popular in-silico method for identifying lead molecules is virtual screening, which looks through chemical and pharmacological databases for an active lead. There are two categories of virtual screening methods: ligand-based and structure-based. In structure-based virtual screening, the target protein's three-dimensional structure is used to screen against chemicals found in chemical compound databases using molecular docking studies. The docking method is used by structure-based virtual screening techniques to find the active lead based on the compound's binding affinity with the target protein and functional effective scores.[14]

Potential inhibitors for OXA-10 ESBL-expressing *P. aeruginosa* were screened using the structure-based virtual screening method against the millions of chemicals found in the ZINC and PubChem compound databases.[30] Additionally, it was used to find new inhibitors of cefazoline-resistant methicillin-resistant *Staphylococcus aureus* (MRSA) Penicillin binding protein 2a (PBP2a). The virtual screening was conducted using the Dock blaster server/discovery studio software.[31, 32] The various approaches used in the virtual screening procedure are illustrated in Figure 5.

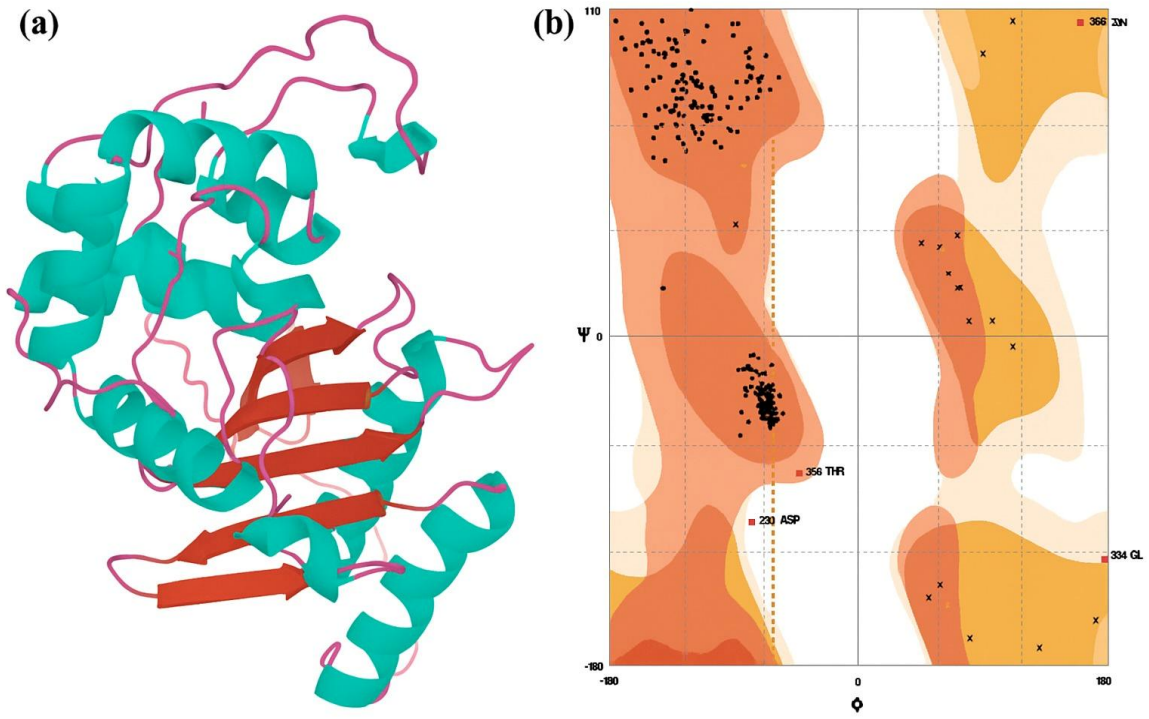

Figure 5. Homology modelling of protein. Malathi and Ramaiah (2018).[14]
(a) OXA-143 CHDL structure (b) Ramachandran plot

II. CONCLUSION

Bioinformatics is a virtual data driven branch of science, with many of the algorithms or tools, software's and databases developed or adapted in response to new types of data. Probiotics' vital function in nutrition, health, and illness has made them more significant from a scientific and commercial standpoint worldwide. Our understanding of how the gut microbiota affects health and illness will be improved by developments in modeling and analysis, which will enable us to modify present and future preventative and therapeutic approaches. One of the most important steps in drug discovery is identifying the drug target. Affinity-based models have given way to phenotype-based models as knowledge and technology have advanced.

REFERENCES

[1] Shreiner AB, Kao JY, Young VB. The gut microbiome in health and in disease. Curr Opin Gastroenterol. 2015;31(1):69-75.

[2] Carter J, Bettag J, Morfin S, Manithody C, Nagarapu A, Jain A, Nazzal H, Prem S, Unes M, McHale M, Lin CJ, Hutchinson C, Trello G, Jain A, Portz E, Verma A, Swiderska-Syn M, Goldenberg D, Kurashima K. Gut Microbiota Modulation of Short Bowel Syndrome and the Gut-Brain Axis. Nutrients. 2023;15(11):2581.

[3] Bettag J, Po L, Cunningham C, Tallam R, Kurashima K, Nagarapu A, Hutchinson C, Morfin S, Nazzal M, Lin CJ, Mathur A, Aurora R, Jain AK. Novel Therapeutic Approaches for Mitigating Complications in Short Bowel Syndrome. Nutrients. 2022;14(21):4660.

[4] Verma H, Verma A, Bettag J, Kolli S, Kurashima K, Manithody C, Jain A. Role of Effective Policy and Screening in Managing Pediatric Nutritional Insecurity as the Most Important Social Determinant of Health

Influencing Health Outcomes. Nutrients. 2023;16(1):5.
[5] Thaiss CA, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. Nature. 2016;535(7610):65-74.
[6] Zhao Q, Elson CO. Adaptive immune education by gut microbiota antigens. Immunology. 2018;154(1):28-37.
[7] Zhernakova DV, Wang D, Liu L, Andreu-Sánchez S, Zhang Y, Ruiz-Moreno AJ, Peng H, Plomp N, Del Castillo-Izquierdo Á, Gacesa R, Lopera-Maya EA, Temba GS, Kullaya VI, van Leeuwen SS; Lifelines Cohort Study; Xavier RJ, de Mast Q, Joosten LAB, Riksen NP, Rutten JHW, Netea MG, Sanna S, Wijmenga C, Weersma RK, Zhernakova A, Harmsen HJM, Fu J. Host genetic regulation of human gut microbial structural variation. Nature. 2024;625(7996):813-821.
[8] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. Cell. 2023;186(2):243-278.
[9] Zhang C, Liu H, Sun L, Wang Y, Chen X, Du J, Sjöling Å, Yao J, Wu S. An overview of host-derived molecules that interact with gut microbiota. Imeta. 2023;2(2):e88.
[10] Alberdi A, Andersen SB, Limborg MT, Dunn RR, Gilbert MTP. Disentangling host-microbiota complexity through hologenomics. Nat Rev Genet. 2022;23(5):281-297.
[11] Lee JY, Tsolis RM, Bäumler AJ. The microbiome and gut homeostasis. Science. 2022;377(6601):eabp9960.
[12] Sharp C, Foster KR. Host control and the evolution of cooperation in host microbiomes. Nat Commun. 2022;13(1):3567.
[13] Afzaal M, Saeed F, Shah YA, Hussain M, Rabail R, Socol CT, Hassoun A, Pateiro M, Lorenzo JM, Rusu AV, Aadil RM. Human gut microbiota in health and disease: Unveiling the relationship. Front Microbiol. 2022; 13:999001.
[14] Malathi K, Ramaiah S. Bioinformatics approaches for new drug discovery: a review. Biotechnol Genet Eng Rev. 2018;34(2):243-260.
[15] Xia X. Bioinformatics and drug discovery. Current topics in medicinal chemistry. 2017;17(15):1709-26.
[16] Zhang S, Liu K, Liu Y, Hu X, Gu X. The role and application of bioinformatics techniques and tools in drug discovery. Front Pharmacol. 2025; 16:1547131.
[17] Patil VM, Masand N. Natural Product Databases and Tools for Anti-cancer Drug Discovery. Mini Rev Med Chem. 2021;21(18):2764-2777.
[18] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. Cell. 2023;186(2):243-278.
[19] Pepke ML, Hansen SB, Limborg MT. Unraveling host regulation of gut microbiota through the epigenome-microbiome axis. Trends Microbiol. 2024;32(12):1229-1240.
[20] Kim HJ, Li H, Collins JJ, Ingber DE. Contributions of microbiome and mechanical deformation to intestinal bacterial overgrowth and inflammation in a human gut-on-a-chip. Proc Natl Acad Sci U S A. 2016;113(1):E7-15.
[21] Nichols RG, Davenport ER. The relationship between the gut microbiome and host gene expression: a review. Hum Genet. 2021;140(5):747-760.
[22] Tulloch LB, Menzies SK, Coron RP, Roberts MD, Florence GJ, Smith TK. Direct and indirect approaches to identify drug modes of action. IUBMB Life. 2018;70(1):9-22.
[23] Schenone M, Dančík V, Wagner BK, Clemons PA. Target identification and mechanism of action in chemical biology and drug discovery. Nat Chem Biol. 2013;9(4):232-40.
[24] Zheng XS, Chan TF, Zhou HH. Genetic and genomic approaches to identify and study the targets of bioactive small molecules. Chem Biol. 2004 May;11(5):609-18.
[25] Katsila T, Spyroulias GA, Patrinos GP, Matsoukas MT. Computational approaches in target identification and drug discovery. Comput Struct Biotechnol J. 2016; 14:177-84.
[26] Sliwoski G, Kothiwale S, Meiler J, Lowe EW Jr. Computational methods in drug discovery. Pharmacol Rev. 2013;66(1):334-95.
[27] Rasul A, Riaz A, Sarfraz I, Khan SG, Hussain G, Zara R, Sadiqa A, Bushra G, Riaz S, Iqbal MJ, Hassan M. Target identification approaches in drug discovery. InDrug Target Selection and Validation 2022 May 18 (pp. 41-59). Cham: Springer International Publishing.
[28] Owens J. Determining druggability. Nature Reviews Drug Discovery. 2007;6(3):187-.
[29] Cheng AC, Coleman RG, Smyth KT, Cao Q, Soulard P, Caffrey DR, Salzberg AC, Huang ES. Structure-based maximal affinity model predicts small-molecule druggability. Nat Biotechnol. 2007;25(1):71-5.

[30] Malathi K, Ramaiah S. Molecular Docking and Molecular Dynamics Studies to Identify Potential OXA-10 Extended Spectrum β-Lactamase Non-hydrolysing Inhibitors for *Pseudomonas aeruginosa*. Cell Biochem Biophys. 2016;74(2):141-55.

[31] Irwin JJ, Shoichet BK, Mysinger MM, Huang N, Colizzi F, Wassam P, Cao Y. Automated docking screens: a feasibility study. J Med Chem. 2009;52(18):5712-20.

[32] Lavanya P, Ramaiah S, Anbarasu A. A Molecular Docking and Dynamics Study to Screen Potent Anti-Staphylococcal Compounds Against Ceftaroline Resistant MRSA. J Cell Biochem. 2016;117(2):542-8.