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Address: 3rd Floor, No. 2, Italia Street, Tehran, Iran

Postal Code: 1416673744

E-mail: info@personalizedmedicinejournal.com

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Personalized medicine Related to Gene Therapy, Ethics

Parham Pooladgar [1 *]

[1]School of Medicine, Shahid Beheshti University of Medical Sciences

**Corresponding author: Parham Pooladgar, School of Medicine, Shahid Beheshti University of Medical Sciences. Email: parhampooladgar@sbmu.ac.ir*

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Abstract:
Gene therapy, as an experimental therapy, is applied for the treatment of diseases through modification of genes. Gene therapy corrects the mutated genes. Somatic and germline gene therapy are two main types of gene therapy. In germline editing, normal genes are inserted into the human's eggs or sperm, zygote, or early embryo. Therefore, the gene is transmitted to the next generation, but in somatic gene therapy, a normal gene is inserted into somatic cells and corrects the defective gene without transmission to children. Personalized medicine is a novel therapeutic protocol for the prevention and treatment of diseases that considers individuals' responding differences to medications. So, it raises ethical issues. Ethical concerns regarding gene therapy and personalized medicine are as follows: safety, accessibility, cost-efficiency, genetic enhancement, dignity, autonomy, identity, and social discrimination.

INTRODUCTION

Gene therapy is among new treatments accompanied by modification of genetic material. This modification begins with the insertion of exogenous DNA into patients' cells in order to treat genetic diseases (1). Gene therapy can correct the mutated genes or site–specific changes (2). This treatment is performed using and manipulating vectors for transferring extra genetic material to target cells (2). Delivery vehicles (vectors) are usually viral or non-viral, such as plasmid and non-structured ones (2).

Viral vectors are important in gene therapy for the simple invasion to host and target cells and injection into their genomes (2). Viral vectors include retrovirus, adenovirus, and adeno-associated virus (3).

There are multiple protocols in relation to the application of gene therapy including knocking out or inactivating the mutated gene, insertion of a new gene into target cells, and replacing abnormal genes (4).

New technologies like gene therapy and genetic engineering change organisms' genetic material, but gene therapy prevents or treats genetic disorders through the correction of genetic defect. While genetic engineering leads to an increase in the organisms' abilities by making changes in the genes (5). Since 1990, when gene therapy was presented for the treatment of adenosine deaminase deficiency for the first time , gene transfer protocols have been improved and developed for human use in several diseases like inherited disorders mostly single-gene recessive disorders, such as hemophilia, cystic fibrosis, sickle cell anemia, blindness, etc. as well as cancers and some non-hereditary diseases like diabetes mellitus, Alzheimer's disease and etc. (3, 6).

Now, the use of cationic liposome technology is interesting as one type of non-viral gene transfer approach because cationic liposomes can bind to negatively charged DNA or RNA due to their positive charge and enter target cells.

Also, another non-viral vector, namely naked DNA or RNA can deliver the gene to target cells. Plasmid DNA (pDNA) transfers DNA, cytokine, and other genes to cells, such as T lymphocytes (7).

The development of vector systems in gene therapy at in-vivo and ex-vivo levels of gene insertion leads to treatment of the human diseases using gene transfer. In cancer immunotherapy, chimeric antigen receptor (CAR)-modified is applied to treat blood cancer (8). Genome-editing technology edits genes via the integration of the correct gene to a specific genetic locus. Clustered regularly-interspaced short palindromic repeat (CRISPR)–associated systems (CRISPR–Cas), transcription activator-like effector nucleases (TALENs), and zinc finger nucleases (ZFNs) change a DNA sequence via a double-strand break to correct a modified gene. However, these tools should be used safely and effectively (8). An important ethical question is about embryo editing by editing germline mutation (8). Researchers face some challenges regarding successful gene therapy like identification of faulty genes and specific cells underlying treatment, the problem of gene transfer, different vectors with

different efficiency, and ethical issues about somatic and germline gene therapy (9).

Somatic and germline gene therapy are two main types of gene therapy. In somatic gene therapy, gene is inserted into somatic cells to correct abnormal genes of cells. This approach is usually successful and abnormal genes are not inherited by the next generation, but germline gene therapy modifies genes in sperm or ova germline cells, which are inherited by the next generation (10).

Stem cells can reproduce and differentiate into specialized cells including embryonic and adult stem cells (11). Pluripotent embryonic stem cells can produce more than 200 different cells leading to differentiation of three germ cell layers, namely endoderm, mesoderm, and ectoderm (12, 13). Pluripotency of stem cells and their unlimited reproduction has made them be used in regenerative medicine (12). Plasticity of stem cells is referred to the differentiation level to numerous cell and tissue types. Plasticity varies from unipotency to totipotency (12). The aim of stem cell therapy is in line with regenerative medicine because both treatments restore and recover the impaired cells (14). Totipotent cells or blastomeres can generate a whole new organism but pluripotent cells can produce 200 types of tissue. Also, mesenchymal stem cells can generate a small variety of multipotent tissues. When stem cells produce one lineage, it is unipotent. Human gonads involve stem cells called as spermatogonia and oogonia having the potential to produce germ line cells, spermatozoa, and oocytes. Adult stem cells are differentiated cells and can de-differentiate and partially repair injuries of a specific organ (12). Compared to embryonic stem cells, adult stem cells are applied extensively in clinics to generate various cell types and regenerate, repair, and treat organs, such as the heart, as well as cancer and systemic diseases. Mesenchymal stem cells have the capacity to differentiate into many cell types like chondroblasts, osteoblasts, osteoclasts, and other cell types (15). It is hoped that cardiomyocytes can differentiate to the myocardium and promote cardiac function. Humanś myocardium can consist of cardiac myocytes after transplantation into animals.

Embryonic stem cells can reconstruct impaired tissues or cells or change humanś organs because they can construct any cell, tissue, or fetus. Argumentative issues on research about embryonic stem cells are raised because these experiments can lead the loss of humanś embryos. Human cloning and stem cell investigations have negative consequences for gene therapy (16).

There is an important controversy related to gene therapy among scientists about fears associated with gene technology, modified nature, and ethical issues (17). Attention to gene therapy risk, risk acceptability, and side effects of this trial has opened a new light to the use of gene therapy as a safe and proper treatment for patients (10).

The aim of gene editing ethics determines the ethical implications of using gene modification in somatic or germline cells. Germline gene therapy has been considered as a controversial issue in medicine and science centers such as the national academy of sciences (NAS) and Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations". Unintended modification of germ cells from an ethical viewpoint especially in-vivo gene therapy should not be confused genetically (18). Ex-vivo manipulations in genome editing of embryos lead to spontaneous germline alterations and their risks. There are some ethical issues about germline gene therapy, such as practical limitation, lack of achievement in pre-implantation stage of genetic diagnosis ، inefficiency of the current procedures of zygote editing, and lack of efficient procedure for evaluation of the modified germ cell and long-term outcome, such as cancer or developmental side effects (18). Gene therapy is useful for treatment of the patients with a genetic disease or those who have developed cancer and gives a chance to them to live normally. Also, gene editing leads to stable and long-term expression of protein, insertion into right site, and targeting specific cell. In spite of usefulness of this approach, it has disadvantages, such as the lack of proper genetic tests to detect the mutated gene in order to replace it with normal gene, pathogenicity of vectors, immune response against this protocol, and ethical concerns (9).

Transferring genes to the somatic cells is performed in three ways namely, in-situ, in-vivo, and ex -vivo.

Gene is inserted directly into the body in-vivo. When the modified gene is introduced into patients' cells out of the body and is replaced back to the patient's body, it is called ex-vivo gene transfer (19).

In germline gene therapy, normal genes are inserted into a human‘s eggs or sperm, zygote, or early embryo. This procedure causes modification of genetic inheritance and leads to an increase in the genetic variation or treats genetic disease. The value and accessibility of this treatment protocol are not known. However, parents prefer to select the desired embryos based on their genetic variations via pre-implantation genetic diagnosis. Somatic gene therapy is the most important barrier to germline gene therapy (20).

Somatic Cell Gene Therapy, Ethical and Social Concerns

Bioethics mainly focuses on genetic engineering. Gene therapy for the treatment of human diseases has resulted in public debate. It both brings about new and worst fears in genetics including the questions raised about" playing God". Many people believe that somatic cell gene therapy is a proper therapy because it provides new sights to produce medications with a low cost (19). Safety and efficacy are very important in somatic cell gene technology when it comes to ethical concerns and should be addressed in the production of drugs and devices, the right selection of patients for the clinical trial, treatment security, protection of privacy, and confidentiality of medical information, and the voluntary option of the procedure must be explained to patients (21).

Germline Gene Therapy and Ethical Issues

There is a debate on germline gene therapy because offspring or the next generation inherits the modified

and transferred genes introduced into sperm or eggs. There is a big question about this intervention, whether a new type of eugenics or genetic enhancement is in germline gene therapy, or whether genetic manipulation in the genetic material of the unborn baby can be acceptable.

Also, there is another debate about the application of germline gene therapy in medicine exclusively or its other application in genetic enhancement, which is the production of the new human being (22). The strong effect of germline gene therapy on future generations, has caused its use to be forbidden in most countries.

There are some complex interactions between human evolution, and social and cultural considerations leading to designing responsible programs for germline gene therapy (23). Two proofs should be considered for this treatment: ethics and safety. The use of ribozymes, RNA-DNA hybrids, etc. is useful for in-vitro fertilization and improves intelligence traits, or contributes to generating the "designer baby" (24). Also, when germline editing eliminates genetic mutation, it can cause harm to the next generation (25). This ethical difference raises the major questions:

Do we have enough information about the effects of long-term treatment, benefits or harms, and side effects?

What is our task regarding the rights, health, chances, and options of the future generation? (25).

Personalized Medicine

Personalized medicine is a novel therapeutic protocol for the prevention and treatment of diseases that considers individuals' responding differences to medications. Personalized medicine advancement resulted in tailored, potent, and proven treatments for specific features of persons, like an individual's genetic makeup, or the genetic profile of an individual's cancer. One of the most personalized medicine is autologous cell therapies in which the patient's own cells are transplanted to the patient. Personalized medicine is a tailored approach based on the right patient, the right treatment, the right dose, and the right time (26).

Today, it was known that patients who have similar symptoms may have different diseases and respond differently to drugs. Discovering and using of conventional treatment for diseases like cancer proper to the patients' features are the main aim of personalized medicine (27).

Recently, patients with genetic diseases like cystic fibrosis and Duchenne muscular dystrophy can be treated by new drugs. These medications targeted specific genetic variants, but these medications gave a better quality of life to the patients. However, individualized cancer drugs have been designed for patients with particular genetic mutations (27).

Also, the term individualized medicine, according to the National Cancer Institute defines information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease. Personalized medicine uses from analysis of genomic data for the prediction, prevention, and treatment of human disorders. Genomic medicine or precision medicine is also recognized as personalized medicine. Today, small- and large-scale genomic databases apply in the healthcare system in numerous countries such as the UK (28).

Using of progresses in genomic techniques has caused the marketing of innovative diagnostic approaches for the investigation about therapeutic outcomes in patients. The deep belief of personalized medicine is that the molecular, physiological, and behavioral characteristics of persons are unique. So, they must take tailored drugs and therapeutic approaches. Recently, tests such as genome sequences and genome- wide analyses applying microarray and next- generation sequences determine DNA sequence variants related to common diseases for individual condition risk estimation, and treatment. Direct-to-consumer (DTC) DNA testing presents valuable information about personal genetic make-up such as single nucleotide polymorphisms (SNPs) directly to the users (29).

Personalized Medicine and Medications

The effectiveness of medications with slightly side effects can be increased by genetics. So, the personalized protocol uses genetic factors to be familiar with the patient's information about responding to a drug as "pharmacogenomics". Pharmacogenomics designs new efficient, safe drugs with proper doses based on a patient's genetic material (30).

One of important field of personalized medicine is pharmacogenomics. Numerous factors such as genomics, epigenomics, the patient's features including gender, ag, and the environment effect on interindividual variability to medication response (31).

Analysis of the drug-target network shows that more presently applied drugs include numerous targets and off-target effects. Sequencing, epigenomic profiling and metabolomics as Genome –wide approaches will be needed for recognize the molecular structure of disease etiology and medication response. Genome-wide studies (GWAS) involved novel biological pathways, but this protocol has drawbacks because many variants with clinical phenotypes like dug side effects are not causative (31).

Ethical Issues

Gene modification for therapeutic goals raises ethical concepts because new treatments, such as gene therapy have risks in spite of great benefits for patients cure. Principles of autonomy, dignity, identity, beneficence, and non-maleficence, which are essential for medical ethics, may be controversial. Cloning and germline gene editing are important regarding ethical concepts. Also, eugenic objects and genetic enhancements improving the traits like height and intelligence could be used for treatment of fetal diseases. Moreover, gender selection, embryo chimerization, psychosocial irregularity of the manipulated human, and genetic disassociation have been discussed in relation to ethical issues (32, 33). Prevention of disability and weakened human growth in every society has been considered notably during the last century. Screening, prenatal diagnosis ,pre-implantation genetic diagnosis

(PGD) ,and assisted reproduction techniques (ART) have induced a new constitution proportional to new demands in society but moral and ethical issues about using these procedures have not been addressed (33). Also, there is a debate about designing experimental embryos, choosing embryos ,collection of the cryopreserved embryos , identity, dignity ,and benefits, and new technologies like mitochondrial restoration, human cloning, genomic map change, and CRISP/ Cas9 are controversial (33).

Mechanisms of genome editing directly specify DNA sequences via the modified proteins or RNA-protein complexes for specific genes or non-coding region and produce DNA breaks as single or double strand. For instance, a Cas9 protein with CRISPR ‘‘guide RNA can cut DNA strands at specific site leading to editing the mutated or defective gene. Genome editing is one of easy and available tools but it needs to be approved with respect to ethical issues before large-scale application (34).

A policy was established for ethical standards including gene therapy in 1996 by the American society of gene and cell therapy (ASGCT). So, for protection of patients in gene editing therapy, the food and drug administration (FDA) and national institutes of health (NIH) have explained two actions: Gene Therapy Clinical Trial Monitoring Plan and the Gene Transfer Safety Symposia (32).

The ethics of personalized medicine

The ethics of personalized medicine is very important issue because the results of some laboratory tests about a high risk of breast or ovarian cancer estimation in women are incorrect, but they did not expose a risk of cancer. Ethical issues are not restrict to using of genetic information, but can increase acquiring of genetic make up for the addition of science and knowledge (35)

Personalized medicine face to some particular legal and ethical challenges such as data gathering, informed consent, distribution and utility, privacy and popular confidence, and altering situation of patients and social equality. So, it is essential to provide the proper balance between scientific and commercial profits, public health and person rights. Also, the legal and ethical perspectives of gene editing technologies such as germline gene therapy should be analyze and interpret correctly (28).

The Big Question: Future of Gene Therapy and Personalized Medicine

So, finding gene /genes of each disease is important in gene therapy. Genome project has opened new sights to new protocols for diagnosis, treatment, and prevention of diseases.

Likely in the future, chance of treating many human diseases will be increased via gene therapy and it is possible to cure the unborn baby with a genetic disorder (36). However, ethical concepts must be considered in gene therapy along with its consequences.

Personalized or precision face to numerous of challenges by using the persons’ genetic make-up. Because genetically –targeted therapies are pricy and troublesome. The cost of personalized genetic tests and drugs for the determination of different persons’ response to medication are not guarantee. All patients must achieve personalized medicine advances without discrimination and abusing (37).

Since using of sequencing technology becomes usual, information about the molecular mechanism and the genetic background of diseases increases and translates into the as higher data, novel treatment and enhanced chances for programming individualized care and health progression (2).

CONCLUSION

In addition to advantages, gene therapy has also some disadvantages. Gene therapy can cure all the diseases, prevent transmission of abnormal genes to the next generation, and help parents to have healthy children .Although, this therapy can have unknown long-term effects or clinical risks, it can improve human traits, such as height and intelligence without disease and select the desired babies or “designer baby” that may lead to social discrimination. Also, this technology is very expensive and is not cost-efficient.

Many ethical issues are very important in gene therapy and cell therapy field with personalized medicine applications because these approaches lead to changes in humans’ genetic material. Ethical concerns must be considered about determining normal and abnormal genes, cost and accessibility for every patient, social discrimination, clinical risks, toxicity, and cancer.

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Consent for publication

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Availability of data and materials

Not applicable

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The authors declare that they have no competing interests

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PP made the conception of the study. PP wrote the main manuscript and revised the manuscript. The author approved the final version.

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The Protective Effect of Ganoderma Lucidum in Mice-Exposed to Sertraline

Ghazal Ghajari[1*], Arijit Chakraborty[2], Seyed Akbar Moosavi[3], Mahnaz Saremi[4]

[1]Department of Cell and Molecular Biology, Faculty of Biological Sciences, Kharazmi University, Tehran, Iran
[2] Department of Sports Physiology and Nutrition, National Sports University (A Central University), Imphal, Manipur, India
[3]School of Paramedical Sciences, Iran University of Medical Sciences, Tehran, Iran
[4]Reference health laboratory, Ministry of health and medical education

**Corresponding author: Ghazal Ghajari, Department of Cell and Molecular Biology, Faculty of Biological Sciences, Kharazmi University, Tehran, Iran. Email: ghajari.ghazal74@gmail.com*

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Abstract:
The goal of precision medicine (PM) is to provide each patient with the treatment and therapy with the optimum results without significant adverse side effects. PM play an essential role in patient care as well as therapy because it tailores the medicine on the individual basis, thus decreasing side effect associated with the drug administration and expediting the treatment as well . Antidepressant drug sertraline (SRT) is currently prescribed to treat mental disorders. This study aimed to determine how much Ganoderma lucidum protects against SRT-induced testicular damage in mice. Mice were given SRT (at a dosage of 30 mg/kg) orally for 35 consecutive days. For 35 days straight, rats receiving SRT were also given G. lucidum extract (at a dosage of 300 mg/kg). SRT therapy caused immediate testicular injury, as evidenced by the significant degeneration and necrosis of the germ cell lining and an increase in sperm malondialdehyde (MDA) levels. Additionally, evaluation of sperm parameters using computer-assisted sperm analysis (CASA) results demonstrated a substantially lower volume, movement, and survival of sperm in the SRT-treated group ($p < 0.001$). Administering G. lucidum extracts to animals that had received SRT may have reduced their histological changes. G. lucidum significantly decreased spermatozoa's lipid peroxidation, and its antioxidant defenses were strengthened. Finally, G. lucidum protects mice›s testicles from harm brought on by SRT, most likely due to its capacity to inhibit reactive oxygen species.

INTRODUCTION

Generally medical treatments are designed for the average patients in which one dose or a therapeutic strategy fits-all-approch used to treat all aptients that may benift some patients but it might have no effect or induce advese side effects on others. A wide variety of factors in patient lead to differnces in treatment response including age, gender, genetic make up, lifestyle ethnicity and environment. Percisiom medicine (PM) which aslo known as "personalized medicine" is an innovative approch to tailoring treatment and disease prevention that takes into the account diffrences in patients thereby reducing the side effects and enhancing the treatment response. PM can be very usefull in particular disease such as infertility that is associated with a variety of etiological factors. One key focus for determining the proper diagnosis and personalized treatment for each infertile couple is understanding the various molecular and pathophysiologic pathways that lead to their condition (1). Therefore, the traditional one-size-fits-all approach to infertility treatments should be rejected because it is not beneficial to everyone (2). Between 40 and 50 percent of infertility-causing reasons among couples are caused by women, 30 percent by men, and 20 percent by both men and women. Men are directly or indirectly responsible for 30 to 50 percent of infertility cases (3). The etiologic reasons causing male infertility include varicocele, congenital malfunction, urogenital infections, endocrine disorders, immunological issues and drug administrations (4).

Beside the physical disorders , mental dysfunction is also known to have a significant influence on both male and female fertility. The first line of therapy for many psychological illnesses and some non-psychological issues is selective serotonin reuptake inhibitors (SSRIs)

(5). Sertraline (SRT) is one of the 3 SSRIs that often prescribed, and used to treat depression, anxiety, and obsessive-compulsive disorder (6). Impotence is one of the sertraline's adverse effects. Harmful effects on the reproductive system include diminished libido, delayed ejaculation, abnormal bleeding (red patches on the skin's surface), the sensation of breast enlargement or milk secretion in women, and itching skin (7). Moreover production of viable embryos, sperm motility, testicular weight, testosterone levels, and spermatogenesis are all decreased by SSRIs (8). There have been limited studies on the harmful side effects of SRT on the male reproductive system. However, prior research suggested that SRT may directly impact testicle tissue function by preventing steroidogenesis and spermatogenesis, eventually resulting in male infertility (9).

It is important to remember that selecting a substance with therapeutic and antioxidant properties is crucial for preventing malfunction caused by SRT. The substance should be able to remove SRT from the body by chelating reaction due to its solid antioxidant components. Ganoderma lucidum is a medicinal mushroom and member of the Payporaceae basidiomycete family that is frequently utilized in traditional Chinese medicine, which usually referred to the «mushroom of immortality» because of its supernatural effects(10). Over 400 bioactive substances that promote health and quality of life are present in G. lucidum(11). Among precious components found in this mushroom are polysaccharides, polyphenols, and triterpenoids, which have a number of biological characteristics, including antioxidant and radical scavenging activity, antitumor, anti-acetylcholinesterase , anti-inflammatory, and anti-aging properties(12). No thorough research has been done on the connection between G. lucidum extract and sertraline testicular toxicity, though the G. lucidum may scavenge reactive oxygen species (ROS) and improve the effectiveness of the innate antioxidant system. Therefore, the objective of this study was to examine the protective effects of G. lucidum on histopathological alterations, and oxidative measures, such as evaluation of sperm malondialdehyde (MDA) levels, as well as sperm quality metrics in mice treated with SRTduring 35 days.

MATERIALS AND METHODS

Chemical

The SRT(Zoloft) provided by Tehran Darou Company, and Iran's Fanavaran kesht Sabz served as the source for the powdered Ganoderma lucidum fruiting bodies.

Preparing hydroalcoholic extract of G. lucidum

To prepare the hydroalcoholic Ganoderma lucidum extract, 300 ml of distilled water and 700 ml of ethanol were used to suspend 150 g of mushroom dry powder. The solution was kept 48 hours at 60°C in the shaker incubator , filtered afterward, and placed in a rotary evaporator to remove the liquid under vacuum until it was completely dried after 48 hours. Total phenolic, triterpenoids, and polysaccharides were evaluated to ensure that 70% ethanol extract solution had high quality. Additionally, the extract's antioxidant activity was assessed.

Measuring the total amount of polysaccharides

The hydroalcoholic Ganoderma lucidum extract's whole polysaccharide content was determined using the phenol-sulfuric acid technique. In a nutshell, 5 ml of concentrated sulfuric acid was added to 1 ml of phenol solution (5%) and 1 ml of extract solution. The solution absorbance measured at 490 nm after 30 minutes as a benchmark, D-glucose was employed.

Total phenol content determination

Folin-Ciocalteu reagent was used to calculate total quantity of phenol and gallic acid utilized as a standard, to perform colorimetric method. 500 ml of folinciocalteu reagent was added to 80 ml of extract solution, and the mixture incubated for 5 minutes at room temperature in the dark. finally 400 ml of a %7.5 sodium carbonate solution was added, incubated for 30 minutes in the dark at room temperature, and absorbance measured at 765 nm.

Measuring the amount of all triterpenes

Using a vanillin-glacial acetic acid solution, triterpenoids were evaluated. After mixing together 0.2 ml of extract, 0.4 ml of 5 percent (W/V) vanillin-glacial acetic acid, and 1 ml of 70 percent perchloric acid solution, the mixture was incubated at 60 °C in water bath for 45 minutes. Following a 15-minute incubation period at room temp, the solution was diluted with 100% acetic acid to a final volume of 5 ml. The absorbance was measured at 548 nm and the ursolic acid solution used as a standard.

Scavenging of DPPH radicals

To assess the antioxidant capacity of the 70% ethanolic extracts of Ganoderma lucidum, diphenyl-1-picrylhydrazyl (DPPH) was utilized as a stable free radical. After diluting the DPPH solution in methanol (1 mM methanol), 1 ml of the resulting solution was added to 1 ml of extract, and the mixture left to sit at room temperature for 30 min. 517 nm was used to measure the absorbance.

Experimental groups

The experiment was conducted by following the

guideline for care and use of laboratory animals. The mice were randomly divided into the following treatment groups: control group (n = 5): the animals were given distilled water by oral gavage dailyfor 35 days and 30 mg/kg of SRT treated group (n=5): animals received 30 mg/kg of SRT orally every day for 35 days. 30 mg /kg SRT and G.lucidum extract treated group (n=5): animals were given oral doses of 30 mg/kg/day of STR and 300 mg/kg/day of G. lucidum extract, respectively. The treatment plan was based on how long the mice›s spermatogenesis took. Animals were slaughtered 24 hours after receiving their final dosage. Testis and epididymis tissues were removed to evaluate the amount of MDA, sperm parameters, and histological alterations.

Examination of the histopathologic alterations

Testicles from treatment groups and control animals were embedded in paraffin after being fixed in Bouin's solution. Hematoxylin and eosin were used to stain tissue sections with 5µm thickness, and light microscopy was used to view them. Morphometric analysis of testis micrographs taken at various magnifications with a microscope, was carried out using digital photographs .

Assessment of sperm parameters

Using CASA technique, epididymal sperm parameters were also evaluated. In this procedure, linearity, curvilinear velocity (VCL), and total motile sperm count were assessed, along with concentration, sperm motility, and hyperactivity (HYP). Whole epididymis was taken out and longitudinally sliced to extract sperm from the caud, and then , the cauda transferred to microtubes containing 1 ml of T6 solution and 25 µl BSA (bovine albumin serum). The microtubes were incubated in 5 percent CO2 incubator (37 °C) for 30 minutes or until spermatozoa formed a sperm suspension.

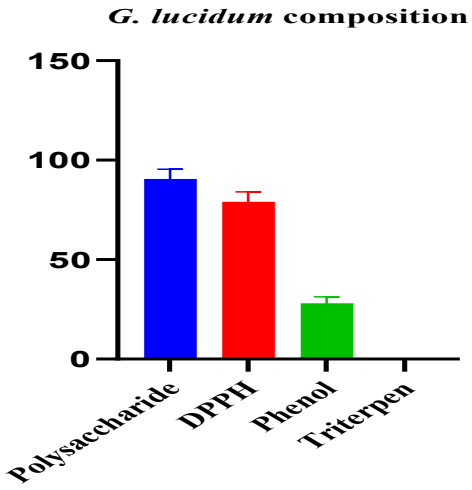

Figure 1. Alcoholic G. lucidum extract›s chemical make-up. By using the phenol-sulfuric acid, folin-ciocalteu, vanillin-glacial acetic acid, and DPPH procedures, the polysaccharides (g/ml), phenols (mg/ml), triterpenes (mg/ml), and DPPH scavenging (percent) activity, were measured respectively.

Assessment of sperm survival

50 µl of the sperm suspension and 50 µl of the 0.5 percent eosin dye were combined in a microtube. After shaking for 30 seconds, 100 µl of nigrosin was added to the initial mixture.A drop of the stained sperm suspension was deposited on slide,covered with coverslip and examined under light microscope using the 400x objective for observation. Live spermatozoa had a blue border, whereas dead spermatozoa appeared purple.

Assessment of malondialdehyde content (MDA)

The levels of lipid peroxidation were assessed according to MDA production . MDA was used as a marker for both production of free radicals and the byproduct of lipid peroxidation, which interacts with thiobarbituric acid (TBA). 400µl of sperm suspension added into 20% trichloroacetic solution was centrifuged at 10,000 RPM for 15 min. The supernatant was combined with 500 µl TBA, 0.1 HCL, and 1.5 ml Tris-KCl buffer, and then heated in a water bath for one hour. 532 nm was used to measure the absorbance of the reaction's end product.

Statistical analysis

One-way ANOVA and Tukey post hoc tests were used to examine the data in SPSS version 19. P value of 0.05 or above was deemed significant. The mean and standard deviation (SD)of all data were displayed.

RESULTS

Compound analysis of G. lucidum extract

The colorimetric technique was used to examine the G. lucidum extracts in 70 % ethanol, and the findings are shown in Figure 1. According to our research, the 70 % ethanol extract included 87 g/ml of total polysaccharides, 25.76 mg/ml of phenols, and 0.0048 mg/ml of triterpenoids. Additionally, a 70 % ethanol extract of G. lucidum had a 82.56 % of total free radical scavenging activity.

Testicular pathology findings

Testicular slices stained with hematoxylin and eosin were analyzed using a light microscope. The histological alterations in the seminiferous tubules and spermatogenic series of the mice treated with SRT and G. lucidum extract are shown in Figure 2. The control mice›s testis anatomy was expected, with mature sperm in the lumen. In contrast, the group that received 30 mg/kg of SRT had decreased interstitial tissue , significant intracellular space, reduction of

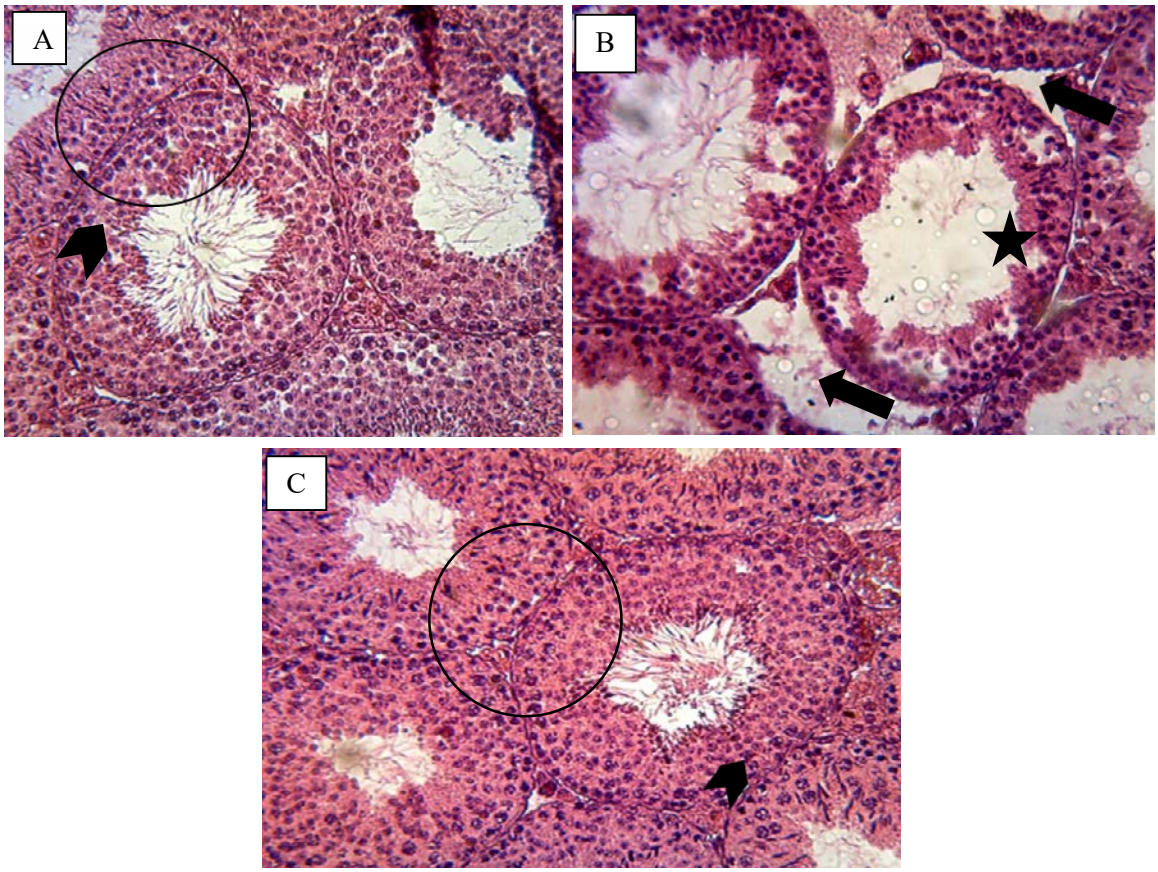

Figure 2. Testicular cross section from mice in the control and experimental groups. Seminiferous tubules with mature germ cells layers were seen in the control and SRT + G. lucidum groups to be normal and active (circle).
These groups showed acceptable intracellular spaces with complete interstitial tissue and seminiferous tubule lumen full of sperm (arrow-head). SRT testicular sections displaying striking changes, a reduced seminiferous epithelium, and an erratic basement membrane (black arrow). Seminiferous tubule lumens were devoid of sperms (star).

Table 1. Sperm parameters before and after being treated with G. lucidum extract and SRT.

Parameters	Control	SRT	SRT + G. lucidum
Volume (mL)	6.55 ± 0.73	2.56 ± 0.8 ****	7.50 ± 0.6***
PR (%)	45.64 ± 6.15	14.44 ± 8.23***	49.2 ± 5.29 ***
NP (%)	14.04 ± 6.38	10.58 ± 6.64	13.58 ± 3.96
IM (%)	38.56 ± 4.15	79.59 ± 8.76****	44.62 ± 10.37 ***
M (%)	60.10 ± 5.15	25.31 ± 10.76***	68.36 ± 9.26 ***
VCL (µm/ sec)	78.46 ± 12.26	42.50 ± 11.96*	62.23 ± 10
VSL (µm/ sec)	29.48 ± 4.68	25.68 ± 4.38	28.32 ± 6.6

PR, progressive, NP, non-progressive, IM, immotile, M, motile, VCL, curvilinear velocity, VSL, straight line velocity, VAP, average pathway velocity

mature sperms in the lumen, tubular and cellular shrinkage, and loss of the entire germinal layer. Seminiferous tubules in the group treated with SRT and G. lucidum (300 mg/kg) were completely normal and spermatogenic. Furthermore, compared to the SRT group, intercellular gaps and interstitial tissue were repaired in the SRT, and G. lucidum treated group. According to the current study, the testicular tissue of 4 mice administered SRT exhibited significant degeneration, atrophied seminiferous tubules, and a lack of differentiated spermatogenic cells that mature spermatozoa in the seminiferous lumen. Also, the

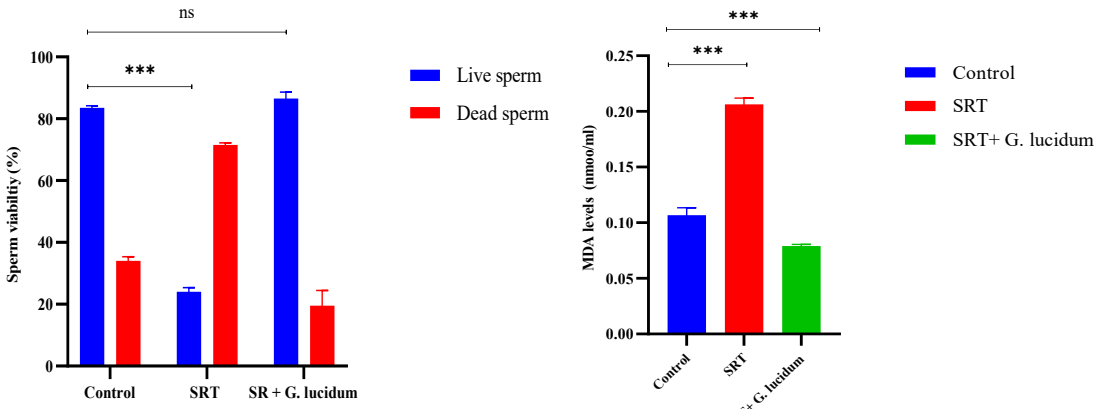

Figure 3. Sperm viability (A) and MDA levels (B) following a 35-day treatment with SRT and G. lucidum. A: significant variations between the control group and SRT was seen. Additionally, there was a significant difference between SRT and G. lucidum (300 mg/kg) assessed (***p < 0.001). B: the MDA levels in 1 ml of mouse sperm suspension after 35 days of treatment with SRT (30 mg/kg), SRT and G. lucidum (300 mg/kg), and control mice. The SRT group sample had the highest MDA level, whereas SRT + G. lucidum had the lowest amount of MDA. Data presented as mean ± SD. (***p < 0.001).

results showed that in 1 mouse, the effect of SRT on the testicular tissue was different from the other 4 mice, along with few changes in the testicular tissue.

Effects of SRT and G. lucidum treatment on mice sperm motility and quantity

The SRT (30 mg/kg/day) group's sperm concentration and mobility (progressive, nonprogressive, motile, and immotile) dramatically reduced, as shown by the CASA ($p < 0.001$). The fraction of immotile sperms significantly increased in the SRT group in comparison to the control group ($p < 0.001$). The co-administration of G. lucidum + SRT group significantly increased the sperm count and motility compared to the SRT group ($p < 0.001$). There was no discernible difference between the control group and the SRT+ G. lucidum group. Table 1 lists further alterations to sperm characteristics.

Effects of SRT treatment on sperm viability

According to Figure 3, eosin- negrosin staining results had significant differences in sperm viability between the control group and the SRT group ($P<0.001$). The percentage of epididymal sperms that were alive decreased after 35 days of oral SRT therapy (30 mg/kg) compared to the control group (27 % ± 2.21). Our results show that the proportion of surviving sperm in the G. lucidum + SRT treatment groups (30, 300 mg/kg) was higher (70 % ± 7.24) than those in the SRT group ($p<0.001$). The outcomes are shown in Figure 3A.

Measuring the MDA levels in sperm

Our findings showed that treatment with 30 mg/kg/day of SRT significantly boosted the generation of epididymal sperm MDA levels (0.276 ± 0.02 nmol/ml, $p< 0.001$) in comparison to the control group. MDA levels in mouse sperm from the SRT + G. lucidum group were 0.766 ± 0.012 nmol/ml, $p < 0.001$, compared to the SRT group. Figure 3B displays the outcomes. Our investigation revealed that 2 mice receiving a dosage of 30 mg/kg of SRT significantly increased their MDA production, whereas the other 3 mice only exhibited a little change. Also, our results showed that treatment with SRT and G. lucidum reduced the production of MDA in 3 mice. In the other 2 mice, the amount of malondialdehyde production was relatively decreased, but not like the control group.

DISCUSSION

The antidepressant drugSRT is most commonly administered to individuals suffer from depression (13)and it is regarded as a reproductive toxin,that may have adverse effects on the human reproductive system (14). In addition, numerous studies have recently been published on the harmful effects of SRT on rat fertility (14,15, 17). Due to the increased need for natural antioxidants in daily life, researchers are increasingly interested in discovering potent natural substances with extraordinary capabilities. It has been established that G. lucidum includes a wide range of bioactive substances that support several therapeutic values for various disorders(16). Therefore, this class of chemicals has been the subject of most investigations. It was, therefore, quite interesting to evaluate G. lucidum's antioxidant capacity in regard to treating the reproductive damage caused by SRT. In the present study, spermatozoa concentration and normal morphology significantly decreased, while sperm MDA levels increased dramatically, and histological abnormalities were observed, in which they all used as indicators of SRT›s reproductive toxicity. SRT treatment also caused a notable decline in the viability of sperm. These results concur with earlier data (17). In this study, the concentration of

sperm was reduced in 3 out of 5 mice in the group receiving SRT. Sperm motility was modestly decreased in 2 out of 5 mice who received 30 mg/kg of SRT. The CASA-based sperm mobility study in the SRT group exhibits a significant drop across all measured motility metrics. Case studies that support our findings show that SRT treated patients had lower spermatozoa volume and velocity but higher levels of abnormal sperm morphology (18, 19). The results of the histological analysis confirmed that SRT could cause seminiferous tubule malfunction and lowering the testosterone levels by damaging Leydig cells. The histopathological results were slightly different among the rats receiving SRT at a dose of 30 mg/kg. The results showed that the pattern of testicular tissue changes in mice was different, which indicate the importance of persolized treatment.

Our results showed that the generation of oxidative stress (OS) resulted significantly greater levels of MDA for the sperm suspension in the SRT treatment group. OS is defined as a situation in which the body creates excessive ROS, that weakens the body's built-in antioxidant defenses (20). ROS includes superoxide anions (O2), hydrogen peroxide (H2O2), peroxyl (ROO), and hydroxyl (OH) (21). Because OS impairs both the structural and functional integrity of spermatozoa, it significantly contributes to sperm dysfunction and considered the leading cause of male infertility (22). Although low levels of ROS are necessary for sperm capacitation and hyperactivation, mature spermatozoa are vulnerable to high levels of ROS that result in lipid peroxidation because of the high concentration of polyunsaturated fatty acids in their plasma membranes and their poor capacity for ROS scavenging due to the absence of cytoplasm (23). Lipid peroxidation thus reduces cell membrane fluidity and permeability, inhibits motility, and finally lessens the ability of mammalian spermatozoa to fertilize (24). Our results showed that the amount of MDA production increased by different level in mices of the SRT group. . The differences in pattern of increase in MDA production in mice can indicate the nessacity of percision and personolized management of treatment.

Also, the results of treating mice with the G. lucidum showed that only 3 mice had a decrease in MDA production. Therefore, based on concept of personalized medicine, we can conclude that antioxidant therapy may have a unique effect for each model, so, each mice's unique conditions should be taken into consideration. Also, the results of the evaluation of sperm viability in the group treated with SRT showed that the survival rate among mice in this group decreased with a slight difference. Nonetheless treatment with G. lucidum extracts increased sperm viability with a specific pattern for each mouse.

According to our findings, Ganoderma lucidum's 70% ethanol extract had significant levels of polysaccharides, triterpenoids, and polyphenols. Recent findings claim that the presence of polysaccharides and polysaccharide-complex compounds distinguishes the G. Luciduim from others (24). The results show that co-administration of G. lucidum extract with SRT at 300 mg/kg/day can reduce MDA production in sperm suspension of 3 mice. According to a specific research, G. lucidum extract increases the activity of the enzymes involved in scavenging ROS , superoxide dismutase (SOD), and catalase (CAT) (25). Additionally, sperm characteristics, including volume and movement in the G. lucidum and SRT-treated groups, were at average level compared to SRT-exposed animals. Examination of testicular tissue slices from both G. lucidum and SRT revealed that the typical shape of seminiferous tubules with several developed cells was present. We propose that SRT, which might affect individuals in different pattern, can be synergistically used with Ganoderma lucidum fungus extract to lessen its adverse effects. Interestingly seminiferous tubules and interstitial tissue repair were visible in photomicrographs taken from both the G. lucidum and SRT groups. By increasing antioxidant activity and reducing lipid peroxidation, G. lucidum may protect against OS and preserve the integrity of tissue functions brought on by SRT, according to the current evidence. However, many causes of male infertility are still unknown. For improved treatment outcomes and efficient drugs administration , physicians should employ tailore the therapy on the individual basis. Additionally, it is essential to evaluate the particular therapy requirements for each individual. Antioxidant treatment, which has been linked to a reduction in male infertility, is sometimes quite successful. Moreover, there must be more study in this field to expand and explore other effects.

CONCLUSION

The current study's findings prove that SRT harms the male reproductive system. More medical research should be conducted for advancement of fertility in in male. This study introduced personalized medicine and its possible treatment for male infertility and also to encourage the and therapeutic measures that are tailored for each individual. This study provides an overview of antioxidant therapy and the identification of biomarkers for male infertility.

Author statement

All individuals who satisfy the requirements for authorship are named as authors, and all authors have reviewed and given their approval to the submitted manuscript's final form. Additionally, each author

attests that they contributed sufficiently to the project, including the concept, design, analysis, and writing, to assume public responsibility for the work's content.

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Pharmacogenomics for Infectious Diseases

Osheen Ansari[1], Imran Hussain[1], Tabrez Jafar[1,2], Farzana Mahdi[1], Israr Ahmad[1,2*]

[1]Department of Personalized and Molecular Medicine, Era University, Lucknow-226003 India
[2]Department of Biotechnology, Era University, Lucknow-226003 India

**Corresponding author: Israr Ahmad, Department of Personalized and Molecular Medicine, Era University, Lucknow-226003-India, Email: ahmadisrardr@gmail.com*

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Abstract:
Pharmacogenomics is the application of genetic and other omics data to specific medication selection and application for avoiding adverse drug reactions (ADR) and increasing drug potency. Pharmacists are playing an increasingly important role in optimizing medicine usage based on genetic testing results. Effect elucidation, genotype-guided medication and modification, medication asset, adverse reaction monitoring, and patient education are all tasks performed by pharmacists. Microbial invasion leads to infectious diseases, which have afflicted mankind from the early era, and is still impacting the health and one of the major causes of morbidity as well as mortality in the society. The response to therapy and the prognosis of an illness are also influenced by an individual's genetic makeup. The data retrieved by genome sequencing of pathogen and humans is one further step forward in examining host-parasite interactions. Consideration of microbial pathogenicity factors, host genetic makeup, and the genetic mechanism involved in disease pathogenesis has paved the way for novel molecular approaches for medications, disease markers, and vaccinations to be discovered. The regulatory approval of amplification tests that are comparable or patronizing to existing gold standard procedures is now assisting the advancement of molecular diagnostics for infectious diseases. Progress in genetics and computation is altering the scale at which biological systems are depicted, and researchers may now expect a precision-focused variety in how they prepare for and respond to infectious diseases. This review will look at the origins and evolution of pharmacogenomics, as well as some of the controversies surrounding its therapeutic applications.

INTRODUCTION

Pharmacogenomics is the study of how genomics and other "omics" play a crucial role to individual differences in therapeutic outcomes characteristics (1-3). The investigation of genetic characteristics that impact a person's pharmacological reaction is known as pharmacogenetics. Pharmacogenomics is the use of genetic data to guide medicine and dosage selection based on a person's genetic composition.

Through a wide range of data, precision and personalized medicine aims to provide a platform for effective health and disease management. Retrospective studies of healthy subject for better understanding of transformation from healthy functional to disease states identify the individuals who are at risk for the disease, as well as suggesting precise treatment based on dynamic and growing data from the sets of both individual trials and population-based studies are all triggering inputs for driving precision medicine (4).

Rapid advancements in biotechnological and informatics techniques, particularly in the domains of genetics, genomics, and proteomics, have surfaced the path for detecting, eliminating the cause, and enhancing human health over the last several decades. Treatment for a patient can only be effective if the condition is diagnosed quickly and the causative agent is identified, which is especially critical in the case of infectious disorders. The discovery of fresh insights into the genome and structural features of pathogen macromolecules has given rise to new hope for the

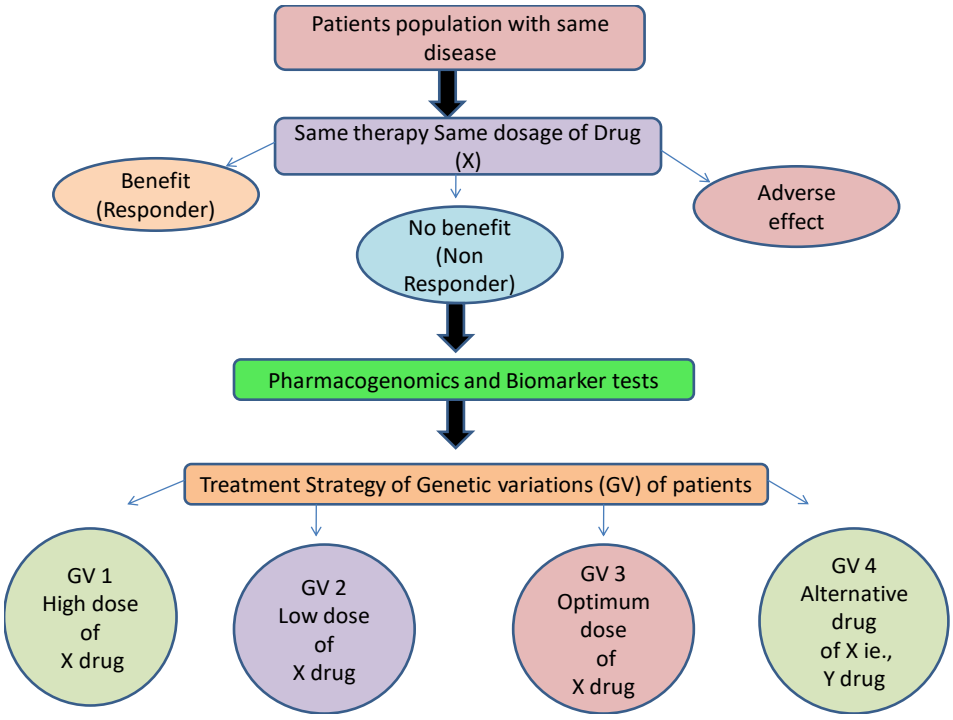

Figure1: Treatment Strategy by Pharmacogenomics

treatment of debilitating illnesses. System biology understanding of microbial diseases is still evolving, and the data provided largely belong to few human diseases. The fast growth of NGS technology has resulted in the creation of a contemporary information system, and with further improvement of such edge cutting techniques in the future era, there is optimism that all illnesses will be eradicated. We will soon have entire sequences of whole transcriptomes, much as we did a decade ago with genome sequences, and proteomic methods shall have the specificity, precision, and sensitivity of microarrays. There are also other techniques in the context of infectious diseases, such as metabolomics, glycomics, lipidomics, and phosphoproteomics, which are still at various phases of development, but we are moving in the correct way (5).

Interactions between the host and the pathogen

Transcriptomics and functional genomics are revolutionizing the concept of illness caused by microorganisms and aiding our research into the causes of infection vulnerability in humans.

Transcriptomics

Scientists have created and applied transcriptomics to improve our understanding of infectious diseases. One of them is cDNA microarray technique widely utilized to investigate the host-parasite interaction. The study focused on the effect of infection on the gene expression of the host cell. The response of the host cell was measured using wild type strain and isogeneic mutant. The key findings of these investigations revealed how pathogen virulence factors alter the expression of host cell components (6).

Functional Genomics

By modifying biological pathways, functional genomics has evolved the technique to understand the pathogenesis of disease. Over the recent decade, RNA interference (RNAi) technology has advanced dramatically, allowing for extensive reverse genetic screening in vivo and model species (7).

RNA interference (RNAi) is a technique that employs to target mRNA sequence using dsRNA with complementary sequence which downregulate the target gene expression. Long sequence of dsRNA may form interferons and other nonspecific reactions in host cells which can be overcome using tiny

interfering RNA or shRNA (small hairpin RNA). RNA interference (RNAi) screening with RNA probes, which causes host genes to lose function, contributed to the discovery of Host Resistance Factors (HRFs). It is made possible when these inhibitory factors are muted, resulting in increased infecting pathogen multiplication. It may also detect Host Susceptibility Factors (HSFs) and permissive factors, which, when muted, reduce pathogen replication. Because of the off-target siRNA impact, RNAi screens still have significant limitations (8). The data must be integrated which is generated from omics technologies to make system biological techniques such as RNAi well efficient in uncovering processes in the host-parasite interaction and hence deciphers cures for infectious diseases. In addition, utilizing transformed pathogens, cellular RNAi knockdowns, or humanized animal models using mice or primate infection models, numerous rounds of biological experiments are necessary. The inferences drawn from the verified data would aid in the development of prediction models, which might lead to a better understanding of the host-parasite interaction.

Infection Susceptibility

A common aspect of many human infections is that only a small percentage of those who are exposed develop clinical illness. For a long time, heritable variables were thought to have a prominent role in explaining inter-individual variations in susceptibility: for example, the early discovery that TB cases concentrated within households led to the belief that tuberculosis was an inherited illness. However, the later identification of bacteria such as Mycobacterium tuberculosis as agents of infectious illness, as well as the experimental proof of the communicable characteristic of diseases, shifted attention to the pathogen (9), potentially overlooking the role of host factors.

It is clear from the history of infectious diseases in humans that not everyone in a particular community gets infected. Both the pathogen's virulence and the host's susceptibility are required for an infective organism to induce an infection. Scientists are working to identify genetic variables that influence the host's innate as well as adaptive immunity and so decide pathogen protection. The genetic determinants and biochemical mechanisms of disease susceptibility have been discovered using animal models of infectious diseases, particularly mouse models (10).

As automated biotechnology and innovative calculation tools evolve, finding genetic signs of natural selection is becoming progressively viable (11,12). The capacity to conduct Genome Wide Association (GWAS) studies and large-scale genetic-diversity valuations has resulted in an exponential rise of publically available genetic data (13), as well as insights into genomic correlation both within and between populations (14-16).

Precision medicine has already revealed critical information about disease causes, biological targets that might stop disease development, and biomarkers that indicate therapeutic response. In response to this common understanding, significant progress has been made in improving patient treatment outcomes (17–19). Personalized medicine will navigate current drug-selection programs such as pharmacogenomics and patient-derived primary cultures (20–26) with current sources of information and consolidation of data.

It is well-known that understanding the pathogen's mode of action and identifying susceptibility genes are critical for disease management in the terms of public health efforts for prophylaxis, diagnosis, detection, and targeting of susceptibility groups in case of an infectious disease.

Pharmacogenomics in the management of infectious diseases

Pharmacogenomics applicability to infectious disorders is still in its early stages. In June 2000, the human genome was fully mapped (27-29). At least 88 bacterial entire genomes have also been sequenced, the majority of which are serious human diseases (30). Researchers can find novel therapeutic targets thanks to the availability of genetic data. As automated biotechnology and innovative calculative tools evolve, discovering genetic signs of natural selection is becoming progressively viable (31-32). The capacity to conduct GWAS studies and large-scale genetic-variation probes has resulted in an algorithmic growth in publically available genetic data (33), as well as

an escalation in genomic correlation both inside and between populations (34–36). These findings highlight the therapeutic importance of discovering natural selection genetic consequences, such as vulnerability loci for infective illnesses that plague mankind (37) and responses when exposed to xenobiotics (38). These breakthroughs have paved the way for precision medicine, which considers a person's genetic statistics when designing clinical care (39,40) and is critical in the quest for individualized or precision medicine. In this respect, genomics offers the ability to advise doctors and accord to precision medicine on various fronts, including illness prognosis, treatment response, and the prophylaxis of adverse drug reactions (ADRs) (41).

Using Genomic Data to Identify Infectious Pathogens

The introduction of large -scale lateral pyrosequencing in 2005 signaled the initiation of the next-generation sequencing era, the first major advancement in sequencing technology after the advent of Sanger sequencing in the 1970s (42,43). The competency of next-generation sequencing increased dramatically in the early years, with yearly sequencing costs diminishing by as much as 80% (44). In public health, these developments were both exciting and intimidating due to the barriers — executing next-generation sequencing may require expenditure in sequencing tools along with cutting edge computing armature to move, store, and analyze large volumes of sequence data (45). Integrating bioinformatics, a relatively new subject in public health, was also critical. Nearly all infectious disease initiatives at the CDC now include pathogen genetics (46).

Antimicrobial Resistance is Determined by Pathogen Genomic Information

Fleming anticipated the possibility of bacteria developing resistance to penicillin shortly after its discovery, and now we know that drug resistance (AMR) has evolved to almost every licensed antibacterial agent introduced. The beneficial function of antibiotics in treating bacterial illness was taken for granted during the golden era of antibacterial discovery, when numerous new groups were found and development of identified groups was quick. Antibiotics help lessen the bacterial infection load. Beta-lactam antibacterials (including penicillin, cephalosporin, and carbapenem), amino glycosides (including tobramycin), tetracycline, macrolides (including erythromycin), glycopeptides (including vancomycin), polymyxins (including colistin), and fluoroquinolones, all was expanded and launched between the 1940s and 1980s (including ciprofloxacin). Pleuromutilins, lipoglycopeptides, and oxazolidinones are three new antibiotic classes that have been introduced since 1990, though several variants of earlier classes have also been introduced. It took around two years to develop drug resistance against the Beta-lactam classes between 1940 and 1990, and nine to 16 years to develop against the other classes. Resistance to the oxazolidinone linezolid has emerged since its introduction in 1990(47).

Using omics technology, the mechanisms of acquiring resistance have been explained. Here are a couple such instances. Fluoroquinolones are antibiotics that inhibit bacterial DNA replication of bacteria by binding to DNA gyrase and topoisomerase, two enzymes involved in bacterial DNA replication. The alteration in the quinolone-binding location in the enzymes indicated overhead causes quinolone resistance in bacteria. A modification in the amino acid at the location of fluoroquinolone attachment to enzymes occurs as a result of the mutation. When both bacterial enzymes are altered, the quinolone antibiotic develops high-level resistance, impacting the prognosis of infection, as opposed to the case when just one of the enzymes is changed (48). Antimicrobial resistance in invading organisms may now be detected via a genetic test. The information is crucial since it will support infection treatment and management. After 24 hours of culture in the presence of oxacillin, the MRSA (methicillin-resistant Staphylococcus aureus) phenotype is observed. Prior to the advent of omics technology, the only way to discover resistance was through a time-consuming culture test. Changes in the penicillin-binding protein PBP2a govern MRSA. PBP2a production is regulated by the gene mecA. In reference laboratories, a polymerase chain reaction assay is utilized to identify the existence of mecA, but a commercially created kit can do so using a fluorescein-labeled mecA probe. When employed for analysis,

both DNA probe and PCR technique may identify the mecA-resistant gene presence within 3 hours. Antimicrobial resistance in infections may be detected quickly, allowing patients to receive appropriate therapy (49).

Infectious Disease Treatment Response is determined by Genomic Factors

The analysis of the host genomics becomes critical in order to properly comprehend pharmacological effects and, as a result, create more effective treatment strategies. The ultimate objective is to understand the system biological effect, but the trend of single gene effects is equally crucial.

The gene producing interleukin-10 (IL-10), a Th2 cytokine, is one of many polymorphic cytokine genes. The development of significant numbers of antibodies is linked to Th2 responses. Th1-stimulating cytokines suppress Th2 responses, and vice versa. Interferon alfa is a drug that stimulates cell-mediated immune responses and antiviral activity to treat chronic hepatitis C. Although interferon alfa is the most common treatment for chronic hepatitis C, reaction proportions are only approximately 50%, especially when combined with other antiviral drugs (50).

The cytokine environment of an infected person can indicate a strong cell-mediated immune response. Patients suffering from chronic hepatitis C who had the IL-10 genetic polymorphism, which results in reduced IL 10 expression, were five times more likely to have a good response to interferon alfa than those who did not have this polymorphism (51). Individuals with a genotype linked to high IL-10 production, on the other hand, were substantially less likely to respond to interferon alfa therapy (odds ratio, 0.22). The IL-10 genotype might be used to predict interferon alfa response. Indeed, an alternative therapy should be developed for those with chronic hepatitis C who have the IL-10 polymorphism, which is linked to increased cytokine production.

Immunologic memory is used in vaccines to create immune response, which protect us against disease in later exposures. To develop protective immunity, the immunological response to the vaccine should ideally mimic the one caused by the natural illness (52-56). Some people who appear to be healthy do not produce an immunological response to a vaccination. A good example is the reaction to the measles vaccination.

A study of healthy school children's antibody responses to the measles vaccination was done (56). Seronegative people were grouped in families, accounting for 10% of the population. This data strongly suggests a genetic influence. The researcher looked for a genetic influence and used HLA genes as a potential gene. Measles vaccination reactions were linked to both HLA class I and class II alleles. HLA-B7, HLA-B51, HLA-DRB1*13, and HLA DQA1*01, all was unified to a positive rejoin for the vaccination against (56-59). Homozygosity for HLA-B, HLA-DR, and HLA-DQA1 was linked to a lack of response to the measles vaccination (56,58).

It is possible that a lack of variety in antigen presentation is to blame for the low vaccination response. Use of vaccines as immune system probes is an innovative way to finding disease susceptibility genes. Vaccines are given to large groups of people. To track down the in general population by using the procedures presented, those who are not able to develop a protective immune response can be compared to those who do.

Infection Treatment: Host Genomics Determines Drug Treatment Response

Drugs used to treat any pathogenic infection can only be effective if we understand how the infection affects the host and pathogen at the genetic level and can explain host efficacy as well as toxicity. We examine a few key infectious diseases where pharmacogenomics research has resulted in a paradigm shift in disease therapy.

Pharmacogenomics in Treatment of Tuberculosis

Several DNA fingerprinting methods have been effective for subtyping Mycobacterial TB since the 1990s (60). Detecting groups of instances that might be linked to current transmission cases that require more intensive examination and possibly intervention is made feasible by identifying closely related strains (61). Whole-genome sequencing allows for considerably better subtyping than was

previously achievable, resulting in greater confidence in the inferred links between instances. Investigators in US TB control programs have now scaled up whole-genome sequencing to sequence isolates from all culture-positive cases countrywide, after utilizing it selectively for several years. Whole-genome sequencing has allowed public health officials in California to rule out more than half of probable outbreaks discovered by traditional genotyping, saving time and resources (Shaw T, California Department of Public Health: personal communication). Primary understanding in tuberculosis programs in the United Kingdom (62), Canada (63,64), and the Netherlands (65) has also confirmed that whole-genome sequencing aids more accurate investigations by extra precisely defining outbreaks (62,63,65), providing insights into transmission undercurrents (39,66), and occasionally indicating the presence of previously unidentified cases or possible "super-spreaders" that should be highlighted for exclusion and cure (62,63). Whole-genome sequencing can also reveal if recurring instances are due to relapse, which offers valuable insights into determining the efficacy of a program (67). Countries which have high disease burden of TB and are also under developed countries, might be in high incidence which bear the brunt amount of the world's TB burden, the ability to prioritize case investigations could be beneficial (68). In these countries, though, a new request of NGS of M. tuberculosis directly from sputum — could play an even more remarkable role (69). Straight sequencing of M. tuberculosis from smear-positive sputum samples is now possible in research laboratory (71-72), but it is expensive and time-consuming for normal healthcare settings usage. If the method can be made applicable in term of its cost effectiveness and practicality, it will allow for quick drug susceptibility inference, which is presently very accurate for most first-line medications and will improve as more data becomes available (70-73). In addition to aiding timely therapy with appropriate drugs, next-generation sequencing will reduce the need for routine phenotypic testing, which is complex, tedious, and difficult to sustain in resource-limited laboratory settings. Meanwhile, in high-income nations, an intermediate technique is already in use: whole-genome sequencing straight from early positive cells, a procedure that reveals drug susceptibility information weeks before standard test results are available (71). State Department of Health New York and Public Health Department, England (70) have received regulatory approval to forego traditional drug susceptibility testing of isolates predicted to be susceptible to all four first-line drugs (roughly 70 to 80% of all isolates) based on whole-genome sequencing (70).

Amplicon sequencing, which includes targeted polymerase-chain-reaction (PCR) amplification of specific mycobacterial genes or marker sequences, followed by sequencing of the amplicons, is another promising option (74). Any sequence-centered strategy for figuring susceptibility should be dependent on the constant updating of databanks containing linked genotypic and phenotypic data to remain relevant over time (72).

Pharmacogenomics in Treatment of Malaria

In 2010 and 2015, malaria occurrence and fatality rates raised by 21% and 29%, respectively (75). Deep sequencing is being used to uncover the genetic background of P. falciparum, the parasite that causes malaria. Polymorphisms, physical and counterfeit number changes, all of which are important for parasite development, are being identified (76). MalariaGEN and other sequencing consortiums help us better understand the genetics of both the Anopheles vector and the plasmodium species. Polymorphism incidences may be utilized as indicators of high recombination rates, which is a key provider to immune evasion and treatment confrontation, according to a current study on genotyping accuracy utilizing in-depth sequencing of Plasmodium parental generations and their offspring (77). A research found 18 deletions in areas encoding multigene families that are linked to immune evasion using whole genome profound sequencing and microarray analysis (78). The investigators discovered chromosomal crossings in six of the deletions and were able to calculate P. falciparum mutation rates (78).

Human genomics has remained under use to find new malaria resistance loci that give 33% protection against severe malaria (79). Transcriptomics and proteomics are increasingly being used to investigate Plasmodium

pathogenesis. The genome-wide translational dynamics of P. falciparum were studied using bioinformatics and statistical models, revealing that parasite transcription and translation are firmly connected, resulting in a wide range of parasite gene expression patterns with great resolution (80). Polysome profiling has been done using ChIP-Seq and RNA sequencing to better understand the control of Plasmodium gene expression in humans. Bunnik et al. 2013 (81) found a delay in peak polysomal transcript profusion for multiple genes relative to the mRNA fraction, which they attributed to non-coding transcript substitute polysomal mRNA splicing processes.

P. falciparum expression patterns have also been described using RNA sequencing, which has discovered unique gene transcripts, substitute splicing processes, and anticipated untranslated sections of certain genes, offering more data on parasite biology (82).

Yamagishi et al. (83) employed RNA sequencing to compare the transcriptomes of the human host and parasite. They found that some human and parasite genetic factors, such as TLR2 (Toll Like Receptors-2) and TIR domain-containing adapter molecule 2 (TICAM2), were linked to clinical manifestations. The transcriptome of P. vivax was also studied using RNA sequencing, which indicated a hotspot of vir genes on chromosome 2, novel gene transcripts, and the existence of species-particular genes (84).

Pharmacogenomics in Treatment of Filaria

Filariasis, along with onchocerciasis and lymphatic filariasis (LF), is a neglected chronic disease initiated by tissue-dwelling nematodes (filariae) which causes considerable health concerns, with a disease burden approaching 86 million people worldwide (85). Onchocerciasis is triggered by Onchocerca volvulus, whereas LF is caused by three parasites Wuchereria bancrofti, Brugia malayi, and Brugia timori (86). Filariasis elimination is difficult in resource-constrained nations due to a lack of sensitive diagnostic instruments, effective therapies, and adequate control measures.

The genomes of W. bancrofti and O. volvulus have been sequenced, allowing for additional genomic research (87,88). Bioinformatics showed the existence of genes coding for host immune system controllers such as human-like autoantigens and serine and cysteine protease inhibitors (91-89).

The filariasis as disease and human as its host, both shall be remained linked together, according to molecular research and computational analysis. Preliminary studies have indicated that LF infections cluster in some families (90,91). These findings suggest that genetic variables play a role in LF infection control, affecting both the presence and severity of microfilariae. However, as with a tropical lymphedema (Podoconiosis) of non-filarial origin, a GWAS would be more thorough in demonstrating this genetic predisposition to Lymphatic Filariasis (92). Note that lymphedema, also known as elephantiasis, is one of the most common symptoms of LF and is caused by a clogged lymphatic system (93). Podoconiosis, unlike LF, is a non-communicable illness caused by soil elements such as aluminium and silica, which are prevalent in volcanic regions (94, 95). A comparative genomics-based investigation of Lymphatic Filariasis might aid in gaining a better understanding of the clinical symptoms.

CONCLUSION

Experience has demonstrated that infectious diseases will arise with greater vigor and ferocity. If diseases are not managed, they will have a significant impact on human wellbeing in terms of mortality and morbidity. Regardless of area, ethnicity, lifestyle, financial class, or ethnic origin, a developing microbial disease-causing infection would affect people's l ives. A s a result, the threat of infectious diseases is very serious, and its prediction as well as management is extremely difficult. In the future decades, major developments in genetics, genomics, and proteomics may be able to meet the challenge. These tools clearly have the prospective to transform the fields of diagnostics, therapy, as well as drug and vaccine research. The time has come to boost public health initiatives at the national and international levels, as well as omics research, in order to fully exploit the promise of systematic innovations that will lead to the era of personalized medicine based on pharmacogenomics.

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Personalized Medicine-Based Microbiology Management of Infectious Diseases

Nasim Fattahi[1], Neda Banaei[2], Naz Tavakoli Lahijani[3*], Ali Rashmanlou[4], Mahnaz Saremi[5]

[1]Department of Biotechnology, Faculty of Biological Sciences, Islamic Azad University of East Tehran, Tehran, Iran
[2]Department of Biology, Faculty of Basic Sciences, Islamic Azad University of North Tehran, Tehran, Iran
[3]Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
[4]Department of Biology, Faculty of Basic Sciences, Islamic Azad University of East Tehran, Tehran, Iran
[5]Reference health laboratory, Ministry of health and medical education

**Corresponding author: Naz Tavakoli Lahijani, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran. Email: naz_tavakoli@yahoo.co*

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Abstract:
This study identified pathogenic variables associated with increased mortality risk in infectious diseases using predictive analysis and a combination of genotypic, phenotypic, and medical data. The quick nucleic acid-based clinical assessment might affect the spread of hospital-acquired illnesses, and we argue that such life-saving operations should be carried out closer to the individual, preferably in 24/7 medical facilities' specialized labs. Personalized medicine notions are relevant in infections for the rapid characterization of a disease-causing microbial community and perseverance of its antibiotic susceptibility characteristic to guide a suitable antibiotic therapy for the proper care of the individual. Personalized medicine aims to interrogate a patient's genetic data as well as pharmacodynamic polymorphisms, and guide drug options and dosage. This work demonstrates the potential use of fundamental genetic analysis in treating infectious diseases and theoretically justifies the value of customized therapy.

INTRODUCTION

Antibiotic usage allows selectively eliminating infectious germs with minor adverse effects on the host cells (1). Every antibiotic therapy is developed based on an individual assessment of the patient (2). Antimicrobial stewardship initiatives to stop the spread of antibiotic resistance have received great attention in recent years (3). Due to the scarcity of novel antibiotic classes, this is especially crucial (4). Antibiotic medications are classified as either empiric (without microbiological inquiry) or definitive (based on the finding of relevant bacterial etiologies and, optionally, in vitro susceptibility testing) (5).

Antibiotics may also be used to prevent atherosclerosis during dental treatments or as preventive medication in various surgical operations (6). Antimicrobial therapy can also be given as a preventative measure to more susceptible patients, such as those with solid or stem cell transplants and blood levels of cytomegalovirus (CMV), those with candida colonization in intensive care units (ICUs), or those with cystic fibrosis (CF) and sporadic Pseudomonas aeruginosa colonization of their airways (7, 8). These are antibacterial drug therapies based on detecting bacteria without clinical signs of infection in the patient populations (9). The threat of colonization with a specific microorganism commonly leads to real infectious disorders with the same pathogen, which are difficult to eliminate, and has thus been an incentive for preventive antimicrobial treatment (10).

A severe illness that causes substantial mortality and morbidity is staphylococcus aureus bacteremia (SAB) (11, 12). The number of cases is now approximately 20% which depends on host and infection variables (13). Age and the existence of concomitant conditions are two host-related characteristics that have repeatedly been proven to be determinants of death in patients with SAB (14). In contrast, the diversity and variability of disease pathogenesis make it challenging to fully understand the involvement of pathogen-specific variables. To resolve this information gap, researchers phenotyped a collection of sequenced medical S.

aureus isolates from SAB patients (11, 15). The researchers discovered pathogen-specific characteristics associated with an increased mortality risk by applying predictive analysis to genotypic and phenotypic information on microorganisms and comparing it to 30-day death certificates (15, 16). This research reveals that an infecting microorganism's genetic make-up may be more relevant to infection progress than previously thought (17). Furthermore, this work presents a model for discovering host-pathogen relationships, where the highest performing predictive algorithm is the one that includes all available information, including clinical data, conceptually proving the advantages of person-centered therapy (18). Further investigation into the effectiveness of targeted medicines or interventions may be sparked by the discovery of significant pathogen-specific characteristics, according to scientists (19).

Personalized Medicine for Infectious Diseases

To offer the proper treatment, at the correct dose, to the particular patient, personalized medicine is a field that employs a patient's genetic information to advise the administration of a suitable treatment protocol in light of the patient's predicted response to a particular drug or mixture of therapies. Personalized medicine ideas have historically been centered on planning genetic conditions, where polymorphisms in genes that control phase are rationally construed against expanding datasets of known medicinal interactions with modified functions to mentor drug medication and dosage (15–19). The value of biomarkers linked to the immune reaction, infection risk, host-microbiota relationships, or sensitivity to antibacterial medication therapy is being established, which is progressively shifting this perspective (19, 20). Use of personalized medicine for infectious illnesses to direct molecular pathogen treatment has clear benefits. The use of a personalized medicine strategy could be conceptualized as a bimodal process for interpreting clinically relevant genomic modules of the patient and the disease-associated pathogen(s) to choose and as well as the treatment regimen for acute life-threatening illnesses. The molecular microbiome provides techniques that enable rapid identification and recognition of microbial cells. This molecular microbiome technique is essential knowledge that a doctor can quickly use to focus the first (critical) hours of a patient's treatment protocol and substantially speed up infectious disease management (21).

Infectious Disease Management in the Molecular Medicine Era

When a feverish, possibly infectious patient enters the healthcare center, a screening cycle including numerous time-consuming processes is initiated. Although, the quantitative phase of the process for traditional phenotypic bacteriology identification techniques represents the most activity occurs constraint, there are also significant delays related to the pre-and post-analytical stages, such as sample transportation, batching procedures, and result transmission, which inevitably lengthen the delivery time (15, 18, 22).

Molecular Tools for POC or near POC Diagnostics of Infectious Diseases

Point-of-care (POC) screening is characterized by medical samples analyzed at or near the individual with the expectation where the test findings will be provided instantaneously or in a very short timescale to aid caregivers with prompt diagnosis and therapeutic action (15-20). This description clearly states that time and space are critical factors on which technology specialists and medical system administrators should work to shorten the detection process and make biological POC screening possible (22). The ultimate aim may be bedside screening, but the creation of near point-of-care laboratories would undoubtedly shorten the detection process and boost the effectiveness of infectious disease treatment by expanding access to highly efficient nucleic acid-based assays (23). In the market for bacterial infections, point-of-care screening is ruled by rapid microscopic examination which can be performed outside medical laboratories but frequently lacks responsiveness and sensitivity (21-23); a frequently updated list of CLIA-waived assessments can be accessed via the Internet (24). Procalcitonin, a potential biomarker utilized in medical care in certain countries, detects the existence and intensity of infectious diseases such as community-acquired pneumonitis and septic (25). Although not particular, and despite some conflicting studies about its reliability and utility as a septic predictive biomarker, it has been proposed that serum prolactin serum concentrations might be utilized as an antimicrobial stewardship strategy (26).

Applications and Anticipated Impact of POC or near POC Diagnostics of Infectious Diseases Increased use of quick diagnostic procedures for infections in healthcare systems in developed and developing nations ensures speedier treatment strategies, more suitable antimicrobial medicine, better human and laboratory asset allocation, as well as decreased mortality, morbidity, and costs (18-21). Depending on the type of health service, the (administrative) modularity of healthcare facility budget procedures is a significant impediment to the implementation of rapid diagnostic techniques when test costs are considered without considering the mid-to-long-term effects of technological advancement on client health and organizational effectiveness (22-25). In this era of rapidly rising medical costs, adopting new technologies and systematic procedures requires careful planning so that the reasoned preliminary choices prove cost

efficiency and clinical usefulness as well as encourage further advancement within microbial identification and infection care organizations (26). This section contains examples of therapeutically meaningful uses of point-of-care or near-point-of-care diagnostic techniques that may act as a standard for customized infection control therapy (27).

A)Bloodstream Infections and Sepsis

Infections caused circulated by the bloodstream are potentially fatal circumstances with a crucial period for timely treatment of fewer than 6 hours. Furthermore, it has been proven that for every hour gained in initiating proper antibiotic medication in individuals infected, the likelihood of survivability improves dramatically (28, 29). The gold standard approach, blood culture, has a very high positive predictive value; however, due to the number and culture-ability conditions of microbial and pathogenic fungi, the overall positive emotion percentage for the prognosis of sepsis is approximated to be 30-40% (30), and possibly as low as 20% (31). Theoretically, detecting MRSA on positive blood samples is quicker than current culture-based approaches. However, the timing of PCR-based diagnosis of MRSA may be far more relevant if the diagnosis was performed straight from blood. Thus, blood culture from each person and checking the microbial density can be a strong point of personalized medicine for treating and managing sepsis in hospitals.

B)Influenza and Severe Respiratory Tract Infections

The treatment of influenza is an ongoing issue in the health service, as diagnostic symptom assessment seldom results in unneeded and inefficient antimicrobial medication (28-31). Antiviral therapy is more efficient than viral therapy when initiated within 48 hours of the onset of symptoms. Nucleic acid-based experiments (reverse transcription PCR) are faster than culture and more sensitive than advertising antigen-based experiments; promoting a non-empirical strategic plan that provides the most significant advantages would seem logical. Similarly, while influenza molecular techniques may offer rapid findings and minimize medication use and hospitalizations, an experimental antiviral medication approach, which costs about the same as RT-PCR, would lead to the medication of 5-15 individuals without influenza for each positive argument (30-32). In a recent publication, molecular analysis has detected other respiratory tract virus pneumonia caused by at least 15 distinct pathogens. The Infectious Diseases Society of North America has underscored the importance of faster molecular diagnostics in this clinical sector (30-32).

C)Hospital-Acquired Infections

Hospital-acquired infectious diseases have become a fundamental problem in medical facilities, with their monitoring being immensely muddled by antibiotic-resistant emergence. It was projected with 1.7 million people having an illness and hospitalized, and nearly 100,000 died. As a result, it led to at least $6.5 billion in medical costs (20-23). Researchers have discussed the significance of reducing the possibility of adverse effects and medication interaction as well as the timing of potential antibiotic therapies in Gram-negative hospital-acquired bacterial meningitis. Rapid computed tomographic molecular techniques might be essential given that nosocomial infection is the second most common illness among hospitalized patients worldwide. That improper first antibiotic treatment has been linked to lower survival rates (32). Fast computed tomography molecular techniques can be a huge step in personalized medicine by choosing the right drugs for patients.

Whole-genome sequencing (WGS) and infectious diseases

The potential use of whole-genome sequencing (WGS) in treating infectious diseases and implementing customized therapy, as shown by this research, is of great interest. WGS will most likely be restricted, given the abovementioned warnings on bacterial pathogenicity's complexity (20, 21, 32).

We predict that, at least shortly, the primary goal of sequence analysis will be quick, ideally culture-free characterization of infectious diseases (22, 33). Time to proper treatment is critical in determining a patient's probability of recuperation for high-burden diseases, such as septicemia. At the moment, screening techniques depend on blood cultures, and further analysis is required to determine the bacterium responsible for the disease and the tolerance pattern, with a turnaround time of two to three days (23, 33). Through sequencing microorganisms directly from a patient's blood specimen, a different diagnostic strategy that uses WGS might be used. In this method, microorganisms from a patient's specimen would be condensed, the Genome would be isolated, and MinI ON equipment would be used for whole-molecule sequencing as genetic analysis (Oxford Nanopore Technologies). The microbial pathogen (including lineage) and the resistance genotype might be identified using sequence data using a well-designed computational laboratory. Additional patient treatment targeting may be made possible by discovering pathogen-specific variables in conjunction with clinical information of medical laboratory during one shift (24, 25, 33).

Dosing patterns for antibiotics and personalized medicine

The positive result for individuals and the antibacterial spectrum has long been understood to be significantly dependent on medication dosage (26, 34). Dosing

Table 1. list a description of several terminologies related to sequencing.

Uses case	Description
Adapter	Any little bit of known-sequence DNA that one attaches to the ends of their unidentified DNA is of interest, often to ultimately enable a sequencing primer to hybridize at this place.
Amplicon sequencing	Analysis of genetic variants using ultra-deep sequencing of PCR products
ANI	An analytical technique that measures the nucleotide identity between genomic areas shared by two isolates is called average nucleotide identity.
Assembly	Genome assembly is assembling a representation of the original genomic sequence from several small DNA sequence fragments, such as those produced by next-generation sequencers.
Bridge amplification	a PCR method where DNA is encased on a solid surface before sequencing. Platforms from Illumina employ it.
Contig	a consensus sequence created by assembling many brief, overlapping DNA segments
cgMLST	Core genome multi-locus sequence typing—an analysis method that detects variation in genes that are present in the majority (>97%) of strains of a given species
Coverage (read depth)	The average number of reads that include a given nucleotide in the reconstructed sequence
Draft genome	Sequencing of genomic DNA is less accurate than the final sequence; some segments are missing, in the wrong order, or are oriented incorrectly.
Emulsion PCR	A polymerase chain reaction (PCR) method on a bead's surface inside of tiny water bubbles floating atop an oil solution. Platforms for IonTorrent take advantage of it.

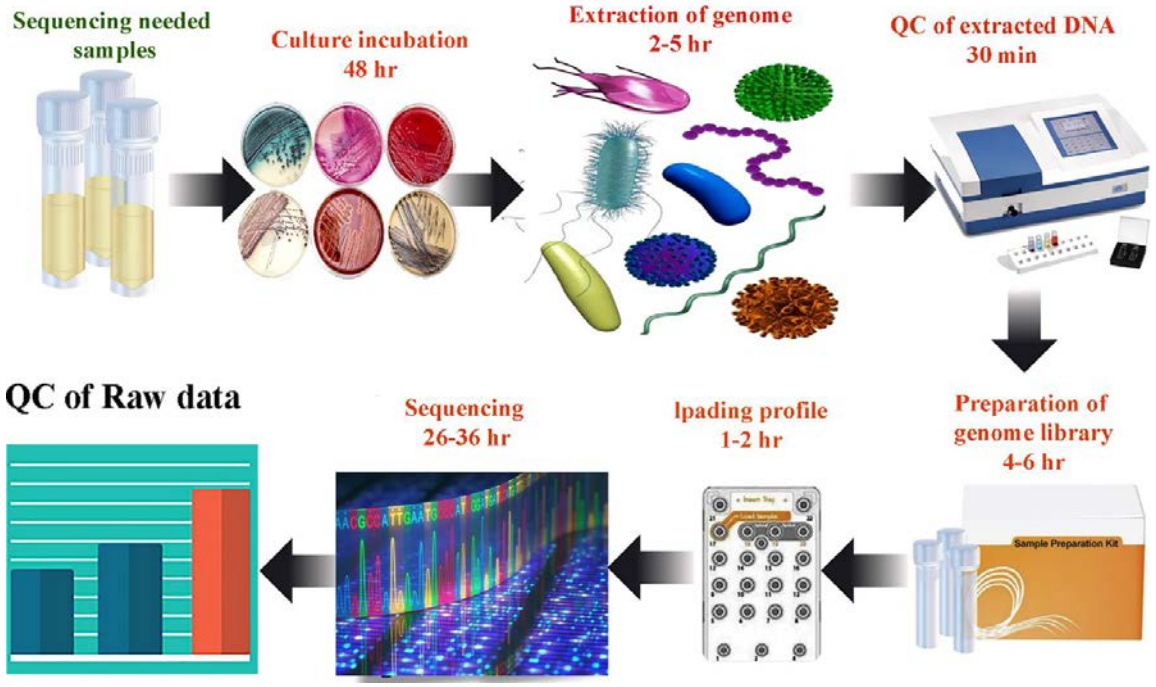

Fig 1. Methodology for full genome sequencing often used in clinical or health promotion labs.

should consider whether the antimicrobial effect is mainly based on duration above the MIC, area-under-the-curve (AUC) above the MIC, or peak dosage above the MIC to achieve the best impact of microbial death or inhibition of microbial contamination (27, 28, 34). The guidelines of current dosage regimens consider this and advocate frequent administration (time-dependent killing), once-daily dosing (mainly density killing), or frequently twice-day dosing (AUC above MIC killing) (29, 30, 34). Most often, if the best antibacterial activities are not considered when deciding on dosage reductions, incorrect dosing with compromised functional status occurs (31, 34).

While altered perfusion and the volume of distribution have received less attention, dosage reductions caused by reduced organ functions are the main focus of pharmacokinetic investigations of critically sick patients. Due to stringent exclusion and inclusion criteria, randomized, controlled clinical trials risk not accurately reflecting the types of patients who will ultimately receive daily treatment with the medicine under investigation (33, 35). Thus, only 13%

of the 187 patients who received tigecycline outside the procedure could have been randomly assigned to the clinical research. Those individuals were noticeably worse than those who had been randomized (32-34).

Quantify level of variety and find mutations that encode tolerance to antibiotics based on personalized medicine

It is crucial to remember that another advantage of such a work process is the capacity to avoid any possible growth "bias" when germs are identified from labeled clinical specimen bottles (34, 35). When cultured under non-selective circumstances (i.e., without medications), this occurs when wild-type populations outcompete specific sub-populations (33-35). These are not only sub-populations probably "hidden," but if separated, they typically occur at a regularity that falls below the detection limit of existing predisposing testing procedures (i.e., less than 1×10^6 organisms). Population diversification has been well-established for viral diseases, with diverse populations linked to worse reactions and outcomes in HIV and hepatitis C infectious diseases (35, 36). Recent investigations have also shown comparable variety in certain SAB cases, which is not unexpected given the development of WGS (36). This finding is important, mainly if the variability that has been recognized is related to the existence of resistant sub-populations since patients who fail preliminary antibiotic treatment typically have persistent septicemia and worse outcomes than patient populations who complete their preliminary SAB. In these situations, WGS would make it easier to quantify the level of variety and find mutations that encode tolerance to many medicines, including daptomycin, and help choose the best course of treatment (37).

CONCLUSION

In this article, we have proposed a personalized medicine method where patients could benefit enormously from optimized infection control influenced by clinically-relevant genomics data derived from microbiota. Genomics data derived from microbiota in specialized POC devices and tests performed near patients or nearby POC research labs and quickly recounted to the attending physician to ameliorate time-consuming and error-prone initiatives occurring in the pre-and post-analytical stages. In addition to the possibilities listed above, it is also feasible that a meta-genomics approach may focus on both host and pathogens variables (from a patient's blood sample), expanding the range of potential treatment targets. A more profound comprehension of mediated activation would be necessary for this and other sequencing technological developments. The following is probably necessary before applying WGS in treating SAB (and maybe other disease types). First, a deeper understanding of the processes behind bacterial resistance is required such as the contribution of a larger genetic context. Regarding the latter, such comprehension may also assist in determining the best kind of treatment (i.e., could predict resistance development). Secondly, further study is needed to understand the extent of bacterial variety that results in clinical failure regarding tolerance.

Ultimately, advances in customized treatment and the control of infectious diseases have saved patients' time, money, and lives. It improves the technologies that enable reliable bacterial DNA recovery (from plasma or tissue specimens) for WGS. In conclusion, despite these factors, WGS is likely to play a significant role.

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Personalized Medicine Approach in the Treatment of Alzheimer›s Disease

Homeira Zare Chavoshy[1], Fereshteh barati[1], Razieh Ghasemi[1*]

[1]Department of Nanotechnology, Jabir Ibn Hayyan Institute, Technical and Vocational Training Organization, Isfahan, Iran

**Corresponding author: Razieh Ghasemi, Department of Nanotechnology, Jabir Ibn Hayyan Institute, Technical and Vocational Training Organization, Isfahan, Iran.Email: Razieh.ghasemi@modares.ac.ir*

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Abstract:
Alzheimer's disease (AD) is a neurodegenerative disease which leads to progressive and incurable cognitive and behavioral disorders. Personalized medicine, which is also called precision medicine, represents an approach to the treatment of the disease with the aim of improving the effectiveness of the treatment, which stops or slows the disease in an optimal and targeted manner at a certain time. It enables the physician to accurately and efficiently identify the most effective treatment. Personalized medicine is based on molecular knowledge. Genome sequencing by the Human Genome Project (HGP) represents one of the most powerful tools for personalized medicine, as along with transcriptomics, proteomics, and metabolomics development which can be used for both disease prognosis and better treatments. In this paper, we will review the strategies that personalized medicine offers for the treatment of AD for the future.

INTRODUCTION

Personalized medicine approach has been used for decades in the management of some rare diseases. Alzheimer's disease (AD) has been the sixth cause of death in recent years, and personalized medicine is a novel approach to preventing and treating the disease with a specific pattern of genetic diversity, environment, and lifestyle factors which contribute to chronic neurological disorders (1).

Dementia is the most common neurodegenerative disease with AD affecting one out of every 10 men and one out of every five women. AD is a devastating progressive neurological disease and is characterized by short-term memory loss, mood swings, and inability to perform daily tasks. Age is one of the main factors for the onset of Alzheimer's disease. AD usually causes plaque formation in the brain's hippocampus, which is responsible for encoding memories, as well as other parts of the brain's cortex that are critical for making sound judgments and decisions. In addition to cognitive impairments such as memory loss, behavioral disturbances can be seen through common neuropsychiatric symptoms such as depression, restlessness, delusions, and hallucinations (2).

Alzheimer's disease, causes and clinical manifestations

According to recent studies, the main cause of this disease is the accumulation of tau protein and the formation of beta amyloid plaques along with neurofibrillary tangles caused by oxidative stress, which is due to the imbalance between the production and accumulation of reactive oxygen species in cells as well as tissues and the detoxification ability of the biological system. Age is the main factor for Alzheimer's disease. Accumulation of beta amyloid plaques is associated with a gradual decline in memory and cognitive function due to the loss of brain tissue (atrophy) (3).

Recognized as the most common form of dementia in the elderly population, AD can manifest itself in two forms: rare early-onset dementia leading to AD (EOAD) before the age of 65 and common late-onset disease AD (LOAD) also known as senile dementia which occurs after the age of 65 due to aging (4, 5).

In 2018, the estimated number of patients of all ages with AD in the US was approximately 5.7 million, with LOAD accounting for more than half of the estimated cases. As the size of the US population over the age of 65 continues to grow, the number of Americans suffering from AD continues to rise, with an estimated number expected to reach 88 million by 2050 (6).

One of the main reasons for the complexity of this disease is the extensive genetic variations involved in AD mechanisms. Along with the progress in human genome sequencing project and bioinformatics tools, many genes mostly associated with the metabolic

pathways of proteins and enzymes of disease have been identified. A list of these genes is provided in Table 1 with some of their references (1, 7).

Despite the identification of these genes, many mechanisms of the AD are still unknown due to the existence of genetic variations, which has made it difficult to develop a definitive drug for the disease (1).

Conventional treatment and personalized medicine

AD is a neurological disorder caused by the accumulation of beta-amyloid plaques in the brain. Various drugs are available that aim to treat AD. For most common pharmaceutical forms, the characteristics of the blood-brain barrier (BBB) must be considered (27). Due to the lack of effective drug therapy for the treatment of AD, only symptomatic treatment is performed for AD patients. Currently, there is no definitive treatment for AD. The medicine available in the market has only the ability to slow down its progress. AD occurs due to excessive production of β-amyloid peptide (Aβ), which is deposited in the brain specifically around neurons which causes the loss of synaptic terminals and neurological disorders in the hippocampus as well as cerebral cortex. It also reduces the amount of certain neurotransmitters such as acetylcholine. Aβ is a peptide derived from the proteolytic cleavage of a membrane protein known as amyloid precursor protein (APP) by β- and γ-secretases (28). APP is an integral membrane protein mainly concentrated in the synapses of neurons and astrocytes. Specific inhibition of β- and γ-secretases can prevent Aβ production. However, this enzymes inhibition can have several side effects for the body (29-31).

In this regard, iAβ5 peptide has been discovered as an anti-amyloid therapeutic agent as a new treatment against AD. By binding to Aβ, iAβ5 peptide inhibits Aβ fibrillogenesis and prevents its further accumulation in amyloid fibrils. However, it was observed that the iAβ5 peptide is unstable and can be easily degraded by proteases. Hence, to construct an iAβ5 derivative with improved properties such as endurance, stability, and higher proteolytic solubility, polyethylene glycol (PEG) and charged sequences can be attached (32). However, this drug has a low level of BBB permeability, which limits its access to the brain.

The treatments that are currently used in AD as a preventive or effective treatment mainly deal with cholinesterase inhibition as well as suppression of glutamatergic signals and ionotropic symptoms including donepezil (Aricept) (33), galantamine (Razadyne) (34) and rivastigmine (Exelon)(35) along with suppression of ionotropic glutamatergic signaling by memantine (Namenda) (36), all of which are prescribed only after the initiation of symptoms. Diarrhea, nausea, and sleep disturbances are common side effects of these drugs.

One of the benefits of pharmacogenomics in neurology includes the use of the drug Plavix, which is included in the category of blood platelet inhibitor drugs. Plavix inhibits the formation of blood clots and prevents strokes in Alzheimer's patients. People who have mutations in the CYP2C19 gene cannot properly metabolize Plavix (27).

The CYP2C19 gene is a member of the cytochrome P450 gene family. Enzymes produced from cytochrome P450 genes play a role in the metabolism of various molecules and chemicals inside cells. The CYP2C19 gene encodes an enzyme in endoplasmic reticulum of the liver, which is involved in processing and transport (37, 38).

Another effective treatment for AD is the use of vitamin E, which has direct effects on the nerves. Vitamin E is an essential micronutrient for the body, with 90% of people being unaware of its effects. Human body cannot synthesize this vitamin and must get it from the diet. Vitamin E is absorbed from the small intestine

Table 1. Main genes and related molecular pathway of AD (1,7)

Gene	Molecular pathway	Ref
APOE, SORL1, CLU, CR1, PICALM, BIN1, CASS4	Amyloid pathway	(8-10)
HLA-DRB5/DRB1, INPP5D, MEF2C	Immune response/ Inflammation	(11-13)
APOE, CLU, ABCA7, SORL1	Lipid transport and Endocytosis	(14-16)
BIN1, CASS4, FERMT2	Tau pathology	(17, 18)
PTK2B	Cell migration	(19-21)
MEF2C, PTK2B	Hippocampal synaptic function	(22)
CELF1, NME8, CASS4	Cytoskeletal function and axonal transport	(23, 24)
INPPD5	Microglial and myeloid cell function	(7, 25)
FBXL7	Phosphorylation- dependent ubiquitination	(26)

(39). According to a study on 3,000 elderly women, those who consumed less vitamin E-containing foods in their diet were mentally weaker (40). With oxidative stress being implicated in the onset of AD vitamin E acts as a major fat-soluble antioxidant. Individuals with intrinsically low alpha-tocopherol plasma levels may be more responsive to vitamin E treatment to combat oxidative stress. Alpha tocopherol is a member of the vitamin E family which is obtained from sunflower oil. Alpha tocopherol is the main type of vitamin E in human plasma. In evaluating the protective effect of alpha tocopherol against oxidative stress caused by bisphenol A in rats, laboratory alpha tocopherol can be used (41).

Over the past years, more attention has been paid to personalized medicine due to the unexpected failure of disease treatment and lack of response in patients or increased side effects in an individual. Also, the use of genetic markers for designing treatments is of great importance.

In a clinical test, the APOE-ε4 allele was selected as a biomarker for early diagnosis of AD using modern biomarker analysis tools (42, 43).

Also, bioinformatics with the wide availability of genome sequence has proved to be a low-cost and comprehensive method for genome analysis in personalized medicine. In personalized medicine, a genotype-to-phenotype relationship is established based on personal genomics information while pharmacogenomics connects the patient genomics information to the specific treatment for him/her. On the other hand, this new field in medicine requires novel analytical tools for analyzing huge amount of data. Thus, the application of artificial intelligence (AI) plays an important role in monitoring the disease-patient relationships, which is very important in early/optimal diagnosis, prevention, and treatment. Predictive algorithms and models are key factors of this innovative field (44).

In an effort to find therapeutic solutions consistent with personalized medicine, the Alzheimer's Prevention Initiative (45), the Dominantly Inherited Alzheimer's Network (DIAN) (46), AD Neuroimaging Initiative (ADNI) (47) and the A4 Trial (48) are presenting mechanisms of Alzheimer's pathogenesis based on clinical trials on patients who have been selected to investigate the performance of the proposed treatments.

CONCLUSION

Due to diverse genetic variations and differences in lifestyle and geographic environment, the causative of Alzheimer's as a neurological disease is still not fully understood. As a result, there is currently no definitive approach for prevention, diagnosis and early treatment of the disease.

The existing therapeutics are also symptomatic treatments that are prescribed from the appearance of the first signs of the disease.

While trying to find ways to prevent and diagnose AD, as well as investigating the genetic variations related to it, personalized medicine has also been implemented in order to provide new approaches for treatment of AD and other rare diseases based on the genetic characteristics, lifestyle, and environment of the patients. Although there is a long way ahead for personalized medicine to overcome this disease due to the existing complexities and the incompleteness of related techniques, in the future, the accomplishments of this field can address many complex problems related to the prevention and treatment of the disease.

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VitminD Treatment Change MTH1 and MYH Genes Expression in HUVEK cell

Naser Gilani[1,2], Mehmat Ozaslan[1], Rozhgar A.Khailany[3]

[1]Department of Biology, Gaziantep University, Gaziantep, Turkey
[2]Farabi Molecular Laboratory, Irbil, Iraq
[3]Department of Biology, College of Science, University of Salahaddin, Erbil, Iraq

**Corresponding author: Naser Gilani, Department of Biology, Gaziantep University, Gaziantep, Turkey, Email: farabilaboratory@yahoo.com*

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Abstract:

Vitamin D (Vit D) ,as an antioxidant contributes to a wide range of diseases including obesity, type 2 diabetes, multiple sclerosis, and certain cancers that oxidative stress plays a vital role in their development. Excessive oxidative stress can damage to DNA and nucleotide pool. Base excision repair and house-cleaning enzymes can protect genome so that any disruption in expression of these genes indicates enhanced susceptibility risk for diseases like cancer. The present study was conducted aimed at evaluating the effect of Vit D on the expression of MYH and MTH1 as DNA repair genes, as well as effect of ViD treatment in Human Umbilical Vein Endothelial Cells (HUVEC) cell line. To do this, bioinformatics tools were used to predict the interaction of MTH1 and MYH with VDR as a specific transcription factor (TF) for Vit D. The cell line was treated with VitD. Next, viability was evaluated using MTT assay. The mRNA expression of MTH1 and MYH was assessed using real-time PCR at 48h post-treatment with Vit D.

Results of the study revealed that Vit D could regulate MTH1 and MYH transcript expression directly through its specific TF; VDR. In response to VitD treatment a different alteration was observed in DNA repair, and non-canonical nucleotide repair genes. Findings of this study showed a new regulation of DNA repair genes in Vit D signaling pathway, and it may be a new perspective for the therapeutic effect of Vit D on related diseases. Variation in interested genes may affect the vitD signaling and personalized medicine should be considered.

INTRODUCTION

It is believed that oxidative stress plays an essential role in pathogenesis of various diseases including cardiovascular conditions such as high blood pressure, atherosclerosis, and strokes, neurodegenerative and autoimmune diseases such as Alzheimer's disease, multiple sclerosis, diabetes, and inflammatory disorder (1). Cancer is developed due to DNA damage, genome instability, and cell proliferation induced by oxidative stress (2). The imbalance between antioxidant defense system and oxidative stress causes damage to lipids, proteins, and nucleic acids (3). Function of DNA repair pathways is responsible for the elimination of endogenous and exogenous mutagens. The ability of this system is vital to reduce damage in the genome and leads to modifying the effect of environmental exposures on disease risk. DNA repair system, especially the Base Excision Repair (BER) pathway, is involved in repairing DNA damages resulting from oxidative stresses. Documents have demonstrated that reduction in efficiency of the BER (4, 5) and house-cleaning enzymes (6) is associated with increased risk of cancer development and progression.

Vit D, as a microenvironment, has wide-ranging effects on different diseases including obesity, type 2 diabetes, hypertension, memory disorders, multiple sclerosis, osteoporosis, autoimmune diseases, and certain cancers. Vit D adequacy leads to the reduction of impairment of DNA repair and protects against oxidative DNA damage (7). Vit D is involved in controlling inflammation, aging process, and minimization of oxidative stress (8, 9). Moreover, Vit D could regulate genes expression via its specific transcription factor,VDR. Few studies have demonstrated the role of VitD in the regulation of expression of DNA repairs genes such as MTH1 and MYH contributing in removal and elimination of oxidative base from DNA (10). To the best of our knowledge, an important gap is whether Vit D is associated with DNA repair genes responding to oxidative stress conditions. In the present study,

we will consider that, whether it exerts its function through VDR. Regulatory effect of Vit D in MYH and MYH promoters that may mediate through VDR was assessed. To find a mechanism, expression of the interested genes were investigated in HUVEK cell line after treatment by VitD.

MATERIALS AND METHODS

Treatment the cell line with VitD

In this study, 1.5×10^5 Huvek cells were cultured in 6-well plate and treated with 100 nM 1, 25-DihydroxyVitD as effective concentration in the biological process(11, 12). After 48h total RNA was isolated and 3 µg of purified total RNA was used for cDNA synthesis (SinaClon First Strand cDNA synthesis Kit). Primers were designed (table.1) and the genes expression was carried out using Real-Time PCR. GAPDH was used as a reference gene. Fold change expression values were calculated using the $2^{-\Delta\Delta Ct}$ method as described by Livak (13). All tests were performed in triplicate.

Determination of cell viability

The MTT assay was used to evaluate viability of HUVEK cells following treatment with VitD. The cells were seeded in 96-well plates at a density of 3.5×10^4 per well and incubated for 48 h after VitD treatment at 37°C and 5% CO2 condition. MTT assay was carried out (Cat. 11465007001, Roche Applied Science, and Indianapolis, IN, USA) according to the manufacturer instructions. Optical intensity was read by a microplate ELISA reader at a wavelength of 570 nm.

Bioinformatics analysis

To identify potential binding sites for VDR in the MTH1 and MYH promoter genes, 1500 bp selected promoter region of MTH1 and MYH were used by ConSite(consite.genereg.net) and JASPAR CORE (http://jaspar.genereg.net/) databases. Screen were predicted with relative profile score threshold 80%.

Statistics analysis

Data analysis was performed using Graph Pad Prism 6 (Graph Pad Software, Inc., San Diego, CA, USA). The difference between groups was compared using either 2-tailed student's t-test or one-waay ANOVA test. P-values<0.05 was considered statistically significant, and data are shown as mean ± standard deviation (SD).

RESULTS

Vit D Treatment Effects on Genes Expression

Genes expression were analyzed treated with VitD . Results showed that expression of MTH1 (2.9 folds, P<0.001) significantly enhanced after VitD treatment, while MYH expression (2.04fold, P<0.05) decreased in comparison with the control cells. Difference in two genes response may due to variation in MYH gene regulatory elements or the difference in the response of its regulatory areas to the concentration of vitD that used in this experiment (figure1).

Cell viability was measured after treatment with VitD. Results showed a decrease by 75% in the growth of the HUVEK cell compared to control group, but it was not a statistically significant (figure2).

The MTH1, and MYH promoters were investigated for VDR binding site. Results of the analysis revealed that there was one VDRE site in the MTH1 promoter sequence located at +361 bp position. Also, in silico mapping analysis in the MYH promoter failed to find any VDRE site.

DISCUSSION

Vit D, as an antioxidant is capable of attenuating oxidative stress in the Central Nervous System (CNS) (14). VitD deficiency contributes to development of different diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis (15), cancer (16), hypertension, and cardiovascular diseases (17). Many of these diseases are related to oxidative stress, which may be regulated through function of VitD and NRF2 (17, 18). Sang -Bum Kim, et al. , in a study explained molecular mechanism of DNA protection against oxidative stress. Our study results revealed that VitD may indirectly regulate the MTH1 promoter directly by VDR TF. But, MYH downregulation may be the secondary or new effects of VitD , in HUVEK

Table 1. specific Primers list for qRT-PCR

Genes	Primer sequence	Product length bp
MYH	F: 5-GTATATGGGCTGGCCTTGGAAG-3 R: 5-CTGTTGGCCCTGATACACACG-3	**141**
MTH1	F: 5-GGGCCAGATCGTGTTTGAGTTCGT-3 R: 5-TCGTCGGGCCACATGTCCTTG-3	**159**
GAPDH	F : 5-CCATGAGAAGTATGACAAC-3 R: 5-GAGTCCTTCCACGATACC-3	**115**

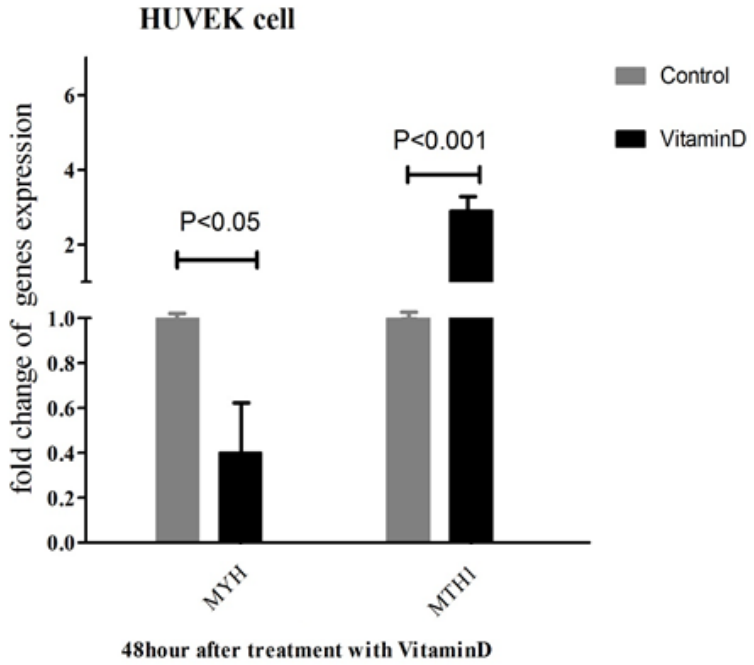

Figure1. The expression of MTH1 and MYH gene at 48 h following VitD treatment in HUVEK cell. Gene›s expression were analyzed by Real-Time PCR and normalized with GAPDH. Results presented as fold change. The presented results are from three biological replicates and three times

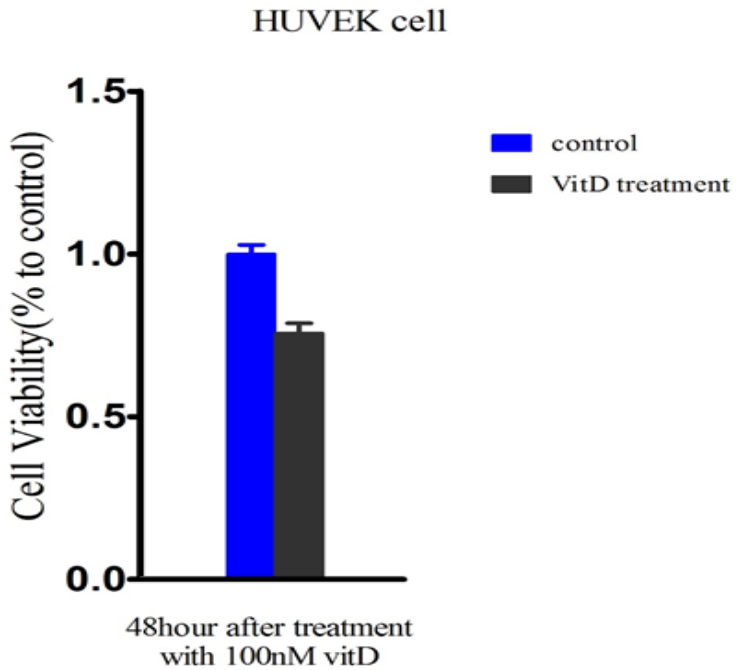

Figure2. Cell viability of Vit D treatment. Cell viability measured by MTT assay in HUVEK cell. After 48 h. The cells growth was inhibited at 48 h after treatment with VitD compare to control Data are mean± SD of three experiments.

cell. Moreover,the presence of putative VDRE in regulatory sequences of MTH1 can explain the direct up-regulation of MTH1 by Vitamin D treatment . These data suggest a possible regulation of MYH gene by another transcription factor or pathway that involve in VD signaling.

MTH1 is responsible for eliminating abnormal bases (19, 20) caused by oxidative stress. This study for the first time, elucidated the interaction between two nucleotide base repair genes and VitD. Our study results also showed that, activity of the interested genes were different at a concentration of 100 nM of Vit D. . In the current study, MYH mRNA levels significantly decreased after simultaneous with Vit D treatment. VDR polymorphisms and Vit D concentrations are important for regulation of ability of the ligand-bound

VDR to bind to VDREs in target gene promoters and initiate second messenger systems. Second messenger systems triggered with Vit D include many intracellular genomic activities and biochemical reactions such as reduction of oxidative stress. Results of a study demonstrated that, physiological concentration of Vit D has different effect on MYH and MTH1 expression. Low concentration of Vit D increases inflammation, and conversely, adequate concentration of Vit D decreases expression of inflammatory cytokines such as Tumor Necrosis Factor-α (TNF-α), and also reduces interpretation of the InsP3Rs and intracellular Ca^{2+} ,and results in acceleration of cellular damage ,apoptosis ,and aging(21). Vit D induces apoptosis in breast, clone, and glia cell lines (22). This result may be explained by the fact that anticancer effect of Vit D was demonstrated in this study, as supported in the study by Sungmin Baek, et al.. In this regard, they reported that a concentration of 10 μM of Vit D significantly reduced viability of studied cell lines; SNU1079, HUCCT1, SUN638, SUN1, whereas, a level of 0.01 μM significantly decreased cell viability just in SNU1079 cell line (23). This data demonstrated that Vit D influences in a dose-dependent manner in different cell lines. Contrary to studies mentioned above, Vertino , et al. demonstrated that Vit D prevents apoptosis in Hela, osteocyte, and keratinocyte cells (24), so, different function of VitD observed in two genes may indicate distinct response of cell in presence of selected concentration.

The previous study showed that Vit D has the anti-cancer effect and reduces cell proliferation (16). Vit D supports the cells against oxidative stress by maintaining normal mitochondrial functions. NRF2/PGC-1α-SIRT3 axis can be activated with Vit D (25). Vit D deficiency can increase oxidative stress. Consequently, accumulation of oxidative stress causes DNA damage and acceleration of cell death (26). Effect of Vit D may be profoundly dependent on the degree of oxidative damage in cell. Although vitamin D can change the expression of genes, the variation in the regulatory regions of genes can influence its signals, so personalized medicine has critical role in this field. Furthermore, the limitation of this study was that the effects of Vit D on expression of genes involved in cell growth, and other DNA repair pathways were not investigated, and future studies are suggested to conduct these analyses.

CONCLUSION

In general, results of the present study emphasized potential role of Vit D in expression of genes involved in DNA and nucleotide repair. These results indicate a new pathway regarding the effectiveness of Vit D in expression of DNA repair genes. In addition, these observations did not imply inconsistency in our study with others, but our findings showed a complementary perspective on function of Vit D.

CONFLICT

The authors have no conflict of interest to declare.

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Excitation Source	8 dye specific LEDs per optical module
Detection Sources	8 photodiodes
Optical Cartridges	SYBR/FAM HEX ROX CY3 CY5 ATTO425 6 slots, swappable optical modules
Dye Selection	Excitation and Emission
Reaction Volume	10 µL to 30 µL
Chemistries Supported	SYBR, Probe, HRM
Thermal System	Six Peltiers made from two ceramic plates with semi-conductor elements, 96-well
Thermal System Temperature Range	25.0 – 99.9°C Heating: 6.0°C/sec Cooling: 3.0°C/sec (Median), 2.5°C/sec (Average) Accuracy: ± 0.2°C or better at typical annealing, amplification, and denaturation temperatures
Dynamic Range	9
Experiment Types	Quantitative PCR with dye, Quantitative PCR with probe, Allele Discrimination with HRM, Allele Discrimination with probe, Comparative Quantitation, User Defined
Uniformity	± 0.4°C
Data Acquisition Time	<3 seconds for all
Cq Uniformity	Cq St Dev <0.20 at fast cycling (5s 95°C/10s 60°C)
Electrical Power (input)	100 – 240VAC, 50/60Hz, 1100VA
Operating Environment	20 – 30°C, 20 – 80% non-condensing humidity, 7500 feet, max altitude
Weight	50 lbs. (23 kg)
Dimensions	19.7" W x 18.1" D x 16.5" H (50cm x 46cm x 42cm)

Feature	Description
Sample Containers	96-well plates, strip tubes; 0.2 mL tubes
Warranty	• 1-year warranty is standard with the instrument • 5-year warranty and service packages available
Onboard Analytics	• Thermal, physical, interactive (sensors) tests • Extended: 125 performance points tested in 30 minutes • Start-up: 59 performance points tested in ~ 1 minute • Optional bypass of both features
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Run Modes	• Stand alone • PC connected • LAN connected to PC (more than 20 instruments can be connected and monitored remotely) • USB connected, external devices
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