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## Proteomic approach in human health and disease: Preventive and cure studies

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### ABSTRACT

Proteomic is a branch of science that deals with various numbers of proteins where proteins are essential human constituents. Proteomic has a lot of functions inside the human and animal living organisms. This review helps to make a thought on the importance of proteomic application in human health and disease with special reference to preventive and cure studies. The human health can be divided into physical and mental health. The physical health relates to keeping human body state in a good health and to nutritional type and environmental factors. The mental health correlates to human psychological state. The main factors that affect the status of human health are human diet, exercise and sleep. The healthy diet is very important and needs to maintain the human health. The training program exercise improves human fitness and overall health and wellness. The sleep is a vital factor to sustain the human health. The human disease indicates abnormal human condition which influences the specific human part or the whole human body. There are external and internal factors which induce human disease. The external factors include pathogens while internal factors include allergies and autoimmunity. There are 4 principle types of human diseases: (1) infectious disease, (2) deficiency disease, (3) genetic disease and (4) physiological disease. There are many and various external microbes' factors that induce human infectious disease and these agents include viruses, bacteria, fungi and protozoa. The lack of necessary and vital dietary rudiments such as vitamins and minerals is the main cause of human deficiency disease. The genetic disease is initiated by hereditary disturbances that occur in the human genetic map. The physiological disease occurs when the normal human function body is affected due to human organs become malfunction. In conclusion, proteomic plays a vital and significant role in human health and disease.

## 1. Introduction

Proteomic is a branch of science that deals with various and huge numbers of proteins where proteins are essential human constituents. Proteomic has a lot of functions inside the human and animal living organisms where the proteomic approach is very important and urgently needed in the new biomarkers discovery and drug treatment

of the disease. Food and nutrition are very important for human health and disease by using proteomic method. This new technique helps for the development of food traceability, sustainability, quality, safety and integrity. The food promotes human health and well-being. There are a correlation between the development of functional foods

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and nutraceuticals in respect to human health and disease[1]. There are 139 antigens detected by human immunoglobulin G antibody using protein microarray technique. From these 139 antigens, 111 antigens were detected in Aotus monkeys. The proteomic method was applied for the development of vaccines against malaria and serodiagnostic tests[2]. There are 376 blood proteins changed in human model of “planned myocardial injury”. Two hundred forty-seven of these proteins were detected in “planned myocardial injury” cases. From these above mentioned proteins, 29 proteins were increased in patients with spontaneous myocardial infarction. The aptamer-based proteomic method helps in biomarker and pathway discovery following myocardial injury[3]. The antibiotic pefloxacin decreases phagocytosis activity, nitric oxide production, large vacuole formation and suppresses interleukin-6, tumor necrosis factor- $\alpha$  and interleukin-1 in animal model. The pefloxacin at higher doses decreases the cell viability of human keratinocyte cell line and peritoneal macrophages of mice[4]. The fetal exposure to bisphenol A delays the lung development and maturation in fetus and increases the susceptibility of childhood to respiratory disease[5]. The proteomic test has many advantages such as: (1) long computation times, (2) decrease of the model performance and (3) the selection of suboptimal proteins. Consequently, there are 7 different proteomic tests were used to evaluate the workflow in cellular protein determination process[6]. The incidence of type 1 diabetes is mainly correlated with viral infections. In coxsackievirus B4, the human pancreatic beta cells are infected. The proteomic tests reveal that proteins are controlled in human pancreatic beta cells in virus infection compared with healthy ones where infection with coxsackievirus B4 is responsible for great decrease in insulin[7]. There are 120 locus-proteins correlated with genome test and another 41 proteins correlated to exome method in proteomic test applied in cardiovascular disease. The majority of these proteins are not detected previously. These proteins loci are responsible for 66% of difference of inter-individual plasma protein level such as human age, sex, and diabetes status variations[8]. The obesity increases insulin resistance and type 2 diabetes incidence. The human diet causes proteomic variations. The diet-induced metabolic syndrome includes (1) disturbance of liver organization and (2) increase of liver cells apoptosis *etc.* Consequently, diet causes liver insulin resistance which increases the incidence and conservation of metabolic disease[9]. The proteomic test of ovarian cancer recorded 4 388 peptides, 104 of these peptides were expressed in the ascites fluid of ovarian cancer. In the benign ovarian conditions, there are double expressed states of peptides where up-regulation of 52 peptides and down-regulation of another 52 peptides were observed[10]. This article aims to focus on the importance of proteomic application on human health and disease with special reference to preventive and cure studies.

## 2. Proteomic

The protein phosphorylation that occurs in cell cycle regulation is the major process inside the living organisms[11,12]. Proteomic has a lot of functions inside the human and animal living organisms and this term was first used by Marc Wilkins in 1994[13]. Proteomic is very important to identify the fetal abnormality of the nervous system

as a result of oral administration of Banxia (Chinese herb used in the treatment of phlegm, cough, and vomiting in pregnant women) in mice. The results obtained showed 1 245 proteins were identified by using liquid chromatography correlated with mass spectrometry (LC-MS/MS)[14]. The proteomic approach is very important and urgently needed in the new biomarkers discovery, diagnosis of systemic sclerosis, disease progress and drug treatment of the disease[15]. In another study, proteomic used to measure the physiological conditions and proteins variations in case of dehydration stress where proteomic test enable detection of 5 727 proteins, from which 211 proteins showed specified modifications[16]. The new technique of proteomic approach such as liquid chromatography correlated with mass spectra (nanoLC-MS/MS) is used to develop a new and detailed diagnostic protocol that helps to identify and prevent cardiovascular diseases[17]. The application of quantitative proteome test is an important and newly technique to identify disease-related proteins. The tissue interstitial fluid is an important and essential key for tumor biomarkers identification[18]. The most important application of proteomic occurs in melanoma which globally records the high mortality rate especially metastatic melanoma which has a high and strong resistance to the ordinary treatment. The proteomic technique includes Orbitrap shotgun combined with mass spectrometry and profound mining proteomic analysis *etc.* These two techniques use the high-resolution reversed phase nano-separation associated with mass spectrometry. These two techniques combined with bioinformatics analysis are very useful in the clinical application and can be helpful for the development of effective medicine of melanoma[19]. Another application of proteomic test is protein characterization of bees' venom. There are 47 proteins occurring in *Bombus humilis* bees' species, 32 proteins in *Bombus pascuorum* bees' species, 60 proteins in *Bombus ruderarius* bees' species, 39 proteins in *Bombus sylvarum* bees' species, and 35 proteins in *Bombus zonatus* bees' species[20]. Moreover, proteomic analysis is reported in both (1) physiological conditions in exercise training program and (2) pathological disorders in obesity associated with type 2 diabetes mellitus. This analysis includes diabetes, obesity, insulin tolerance, diminished glucose uptake and exercise or training program. The results revealed 73 proteins in the muscle of type 2 diabetes mellitus obese patients and these proteins are not observed in exercise training individuals. In exercise training individuals, there is an increase in proteins of the following cycles: (1) tricarboxylic acid cycle, (2) mitochondrial electron transport cycle and (3) mitochondrial respiratory cycle complex I association. There are 5 proteins recorded in obese type 2 diabetes mellitus patients less than that of exercise training individuals[21]. The proteomic analysis is a simple, easy, fast and accurate method to differ male from female through using urine protein content. There are 232 and 226 proteins detected in both male and female urine, respectively. From these proteins, there are 162 proteins which are common in both genders, while 70 proteins are distinct that occur in male and 64 proteins are special to female. From these 162 common proteins, there are 13 proteins that occur in different concentrations in both male and female[22]. There are 6 600 proteins detected in a proteomic analysis in cancer stem cells of osteosarcoma. Consequently, proteomic approach is a good test in osteosarcoma. A label-free quantitative method is applied to analyze differentially expressed proteins. The molecular signals pathways regulate cancer stem cells. The  $\alpha$ -actinin 4 proteins

are identified by Western blot assay. These results help to better understanding of the molecular basis of cancer stem cells and more progress in the treatment of osteosarcoma[23]. The patients with lymphoma and myeloma can use proteomic analysis correlated with mass spectrometry. This method is good and accurate. The patients with rheumatoid arthritis or systemic ankylosing spondylitis or lupus erythematosus should be investigated by proteomic test that depends on matrix-assisted laser desorption/ionization correlated with mass spectrometry. This method is a fast and suitable technique[24].

### 3. Role of proteomic in human health

People are capable of adjusting themselves in response to environment by physical, mental, psychological and social changes[25]. The human health can be divided into physical and mental health. The physical health relates to keeping human body state in a good health and to nutritional type and environmental factors. The mental health correlates to human psychological state while the physical health is affected greatly with mental health and vice versa. Both genetic and environmental factors correlate to complex human characters. The genetic factor represents nearly 50% as well as the environmental factor in human health features. The human feature is not only affected by variation in DNA but also by modifying gene expression[26]. The structure of gut microbiome and the quick process of metabolism of resveratrol diet identify resveratrol metabolites end product. Resveratrol affects cardiovascular risk factors such as an increase in blood cholesterol or in tri-methylamine *N*-oxide levels[27]. In human health, the mean hazard indices of arsenic as an example of environmental factor were below 1. This result proved the absence of non-carcinogenic risk of arsenic. In addition, the cancer danger of arsenic was within the acceptable range (below  $1 \times 10^{-4}$ ), indicating low to very low risk to the exposed population[28]. A complicated and overlapping correlation occurs between sleep-disordered breathing and cardiovascular disease where sleep disorders harmfully affect cardiovascular structure and function. The disruptive sleep apnea is related with an increase in the incidence of heart failure, stroke, and atrial fibrillation and coronary heart disease. Consequently, the continuous pressure recovers the obstructive sleep apnea. Moreover, many clinical observations of continuously treated patient such as sleepiness, quality of life and mood are recorded, in the same time, the intermediate cardiovascular end points such as blood pressure, cardiac ejection fraction, vascular parameters, and arrhythmias are also treated[29]. The metabolomic examination is applied to identify the food ingredients such as lipoic acid, pectin and *Saccharomyces*. These ingredients have a synergistic and complementary role with female and male hormones which play an important and significant role in human health status. These dietary constituents and hormones protect human health against colon cancer and keep human health features[30]. From the above data, it is clear that human diet, exercise and sleep are the main factors that affect the status of human health.

#### 3.1. Role of proteomic in human diet

The healthy supplementary diet is very important and needed to

maintain the human health. The healthy and integrated food stuff should contain both plants' and animals' foods. This food is needed for energy power supply and maintenance of the human physiological process in hemostasis, build-up human muscle and regulation of blood pressure and body temperature. The relationship between diet and human health or disease is very important in both biomarkers discovery and clinical applications. In a study, the proteomic analysis was done after administration with sweetened dried cranberries in urine and feces in a sample of 10 healthy persons. The proteomic analysis depended on mass spectra of different proteins in urine. The oral intake of sweetened dried cranberries induced many changes to urinary 22 proteins and multiple sequences of 16S fecal ribosomal RNA genes which reflect negatively on human health[31]. In another study, proteomic test revealed that low-dose of lyophilized oregano suppressed tumor frequency by 55.5%, tumor incidence by 44%, and tumor volume by 44.5% compared to control animals. Analysis of rat tumor cells showed Ki67 and VEGFR-2 were decreased while caspase-3 expression was increased after low-dose of lyophilized oregano treatment[32]. The huge and very fast advances in the last decade for proteomic researches are of great help to discover the relation between human-related microbes and the role of human immune system. These researches can help in prevention and cure of chronic diseases, including allergy. The advances in proteomic studies are beneficial to understanding the environmental effect on human health and the human effect on all surrounding living organisms which are very important for human health, and this concept can affect health and disease over all human life[33]. The obesity represents major health crisis world-widely. The proteomic studies are associated with brain lipotoxicity that occurs in brain dysfunction in high fat diet. There are major variations of brain proteins which occurred in proteomic analysis based on mass spectrometry. These proteins were mainly correlated to oxidative stress, glycolysis and calcium signaling[34]. The proteomic approach helps to keep the gastrointestinal function and health. The meta-proteomic in addition to real-time PCR and DNA fingerprinting are the essential techniques applied. The human diet with lower fat and higher fiber increased beneficial bacteria activity and fecal fatty acid secretion, especially butyrate, while the human diet with higher fat and lower fiber stimulated another bacteria which have negative effect on human health[35]. In another research, the results obtained showed that inflammatory proteins in liver were larger after saturated fatty acid oral intake than inflammatory proteins in liver after monounsaturated fatty acids oral intake in high fat diet. The dietary administration of the monounsaturated fatty acids in high fat induced an important and significant process of cholesterol moving between the different groups in liver. From these results, it could be concluded that new biomarkers of damaged liver organ were developed and reflected from the reverse cholesterol transport process *in vivo* estimated from protein levels on high density lipoproteins[36]. There is a major variation with both progressive age and profibrotic environment. This could be increased significantly the animate human resistance. These observations were reported recently by using proteomic analysis of lung matrix. There was stimulation of myofibroblasts and transforming growth of factor-beta signaling pathway in case of extra matrix proteins deposition[37].

### 3.2. Role of proteomic in human exercise

The human training program exercise improves or sustains human fitness and overall health and wellness. The exercise supports muscles and recovers the cardiovascular system and human body hemostasis. The changes in quality of food, customs, and exercise increase exposure to obesity. The lazy lifestyle induces dysfunction of blood flow that exerts an effect on cardiovascular function of pregnant women. The nitric oxide synthesis and bioavailability are controlled by the antioxidant activity of endothelial cells. These observations disturb the mother vascular health and vascular performance of the placenta and consequently the healthy development of the fetus and the fetoplacental blood flow. All the above observations are controlled by the proteomic and metabolomic of newborns[38]. This proteomic test is focus on exercise-related proteomic which is characterized by the adenosine triphosphate generation, oxygen delivery, antioxidant activity and regulation of mitochondrial protein synthesis. The powerful and intensive training program controls oxidative phosphorylation and tricarboxylic acid cycle processes inside the human body. The amino acid metabolism and calcium ion leakage into cytosol are controlled by exercise. The proteomic is controlled by exercise style, strength, intensity, schedule and muscle type. These analyses of the molecular networks are controlled by exercise training program in health and disease, and these findings support the therapeutic effect of exercise[39]. The two-dimensional proteomic analysis was performed. The unilateral lower limb suspension induced a reduction of myofibrillar, metabolic (glycolytic and oxidative) and anti-oxidant defense system protein content. The long-term unilateral lower limb suspension did not inhibit the helpful and beneficial effect of exercise on human muscle[40]. The proteomic analysis aims to evaluate extensive and prolonged training exercise in healthy and diseased populations. This exercise decreases lipid while increases enzyme activity and harmful rule of vascular advance. There are differential DNA methylation and microRNA (miRNA) expression changes that occur in skeletal muscle in massive and hard exercise training program[41]. Both exercise and maternal separation stress are done by proteomic technique through isobaric tagging and matrix-assisted laser desorption/ionization tandem mass spectrometry method. Maternal separation stress controls hippocampal proteins occurred in energy metabolism such as enolase, triosephosphate isomerase and nucleoside diphosphate kinase B. Maternal separation stress changes synaptic plasticity proteins such as neurocan core protein, tenascin-R,  $\alpha$ -synuclein, Ba1-667 and brevicin. The exercise stops numerous alterations by inhibiting the secretions of hippocampal proteins related with energy metabolism such as nucleoside diphosphate kinase B, enolase and triosephosphate isomerase. The exercise also stops synaptic plasticity proteins such as Ba1-667, brevicin,  $\alpha$ -synuclein, tenascin-R and neurocan core protein. So, both exercise and maternal separation stresses have conflicting effects on the brain hippocampus proteins[42].

### 3.3. Role of proteomic in human sleep

Sleep is a vital factor to sustain the human health. The sleep is extremely important for growth and development in childhood. The continuing sleep disorder is proportional related to prolonged health

problems. The proteomic analysis reveals that humans with myopes exhibit higher serum melatonin levels than that in non-myopes. This refers to important and essential roles of human light exposure and circadian rhythm in the human myopic growth mechanism[43]. The proteomic technique of red blood cells revealed that obstructive sleep apnea syndrome (OSA) is accompanied with numerous and diverse proteins. The red blood cells samples were taken and collected from patients with moderate and also from severe OSA at pre- and post-night. The mass spectrometry technique identified 31 proteins including 21 unique and different proteins as a result of presence of post-translational modification regulations. The most proteins are associated with catalytic, oxidoreductase, peroxidase, hydrolase, adenosine tri-phosphatase and anti-oxidant activity. At morning a larger number of differential proteins including response to chemical stimulus, oxidation reduction, regulation of catalytic activity and response to stress were observed in OSA[44]. The sleep influence on brain melatonin level where proteomic and genomic studies concern on melatonin 1 and melatonin 2 receptors reveals 378 different proteins. Some of these proteins are presynaptic proteins interacting with melatonin1 receptor, but not with melatonin2 receptor and these observations indicate a major role of melatonin1 receptor in neurotransmission. The melatonin1 receptor presents in the hypothalamus, striatum, and cortex so melatonin1 receptor is part of the presynaptic protein network[45]. The common public health concern that causing and sustaining many harmful effects on metabolic and cardiovascular health is OSA. The progress and advanced proteomic research is needed for identifying novel disease mediators as important diagnostic and therapeutic targets for many diseases, including OSA[46]. The OSA is associated with obesity and diabetes. These complications include dysregulation of metabolic and cardiovascular homeostasis. The complication disorders conditions in obesity and diabetes could be improved by new and advanced techniques such as proteomics analysis which lead to improvement of health outcomes relating to the adverse consequences of OSA and consequently improve the risk of sleep disorders[47]. The recent technique such as proteomic is applied in the OSA. The PCR technique is the most applied technique especially in the field of sleep medicine and provides good and bright insights in the pathological conditions related to OSA, thereby enabling diagnosis and management for this complicated sleep disorder[48].

### 4. Role of proteomic in human disease

The human disease indicates abnormal human condition that has an influence on specific human part or the whole human body. This includes disturbance of human structure or function. There are external factors such as pathogens and internal factors such as hypersensitivity (allergies and autoimmunity) that cause human disease. Any condition that induces human distress, social problems, pain, dysfunction or death is called human disease. Human disease is usually accompanied with human disorders, syndromes, infections, injuries, disabilities, unusual behaviors and abnormal characters. The proteomic study using mass spectrometry technique (nLC-MS/MS) helps to map the proteomic landscape of ultraviolet-irradiated human metastatic-melanoma cells. The data obtained lead to molecular-

network explored double nature of ultraviolet radiation for both anti-tumorigenic and tumorigenic factors in metastatic-melanoma cellular tests. This proteomic technique helps in the development of new biomarkers and expansion of new therapies for the disease[49]. The term “proteome” was used to describe all of the molecular variations formulae in which the protein molecule from a single gene could be occurred. There were various and many efforts that were done to develop techniques for proteome description[50]. In new and recent clinical study, proteomic investigations of the chemokine receptors showed great and major variations that were established and recorded between cells obtained from both chronic lymphocytic leukaemia and small lymphocytic lymphoma patients. Consequently, higher expression of transferring receptors and lower expression of adhesion molecules were detected on chronic lymphocytic leukaemia cells than on small lymphocytic lymphoma cells, so small lymphocytic lymphoma had a more progressive disease than chronic lymphocytic leukaemia[51]. In another study, there are 4 plasma proteins and these proteins: (1) sex hormone-binding globulin (SHBG), (2) apolipoprotein C-1, (3) gelsolin and (4) complement component C4-A are expressed in patients with gastric cancer (GC). The SHBG protein is repeatedly expressed in GC patients and GC patients have higher SHBG levels than the control one. The gender, age, and disease stage influence SHBG levels in the patient group. These results proved that liquid chromatography associated with mass spectra is more suitable for plasma biomarker discovery, and SHBG is a sensitive and accurate plasma biomarker for GC control[52]. The protein structure and function are disturbed in developmental and metabolic disorders occurred after exposure to bisphenol A (BPA) and di-n-butyl phthalate low levels in proteomic tests application. The BPA and di-n-butyl phthalate control the expression levels of multiple proteins which provide us good information for actions of BPA and di-n-butyl phthalate on the developmental systems[53]. The proteomic study was previously applied in Parkinson’s disease where resveratrol treatment was influenced on deregulated specific biological process such as cellular redox balance and protein homeostasis. The resveratrol was also effective at restoring the heat-shock protein network and the protein degradation systems. The resveratrol administration caused an increase in glutathione level while decrease of oxidized glutathione/reduced glutathione ratio and reduced free thiol content in patient cells compared to normal fibroblasts. Thus, resveratrol preserves the cellular homeostasis in *parkin*-mutant fibroblasts[54]. In general, there are 4 principle types of human diseases: (1) infectious disease, (2) deficiency disease, (3) genetic disease and (4) physiological disease.

#### 4.1. Role of proteomic in human infectious disease

There are many and various external microbes’ factors that induce human infectious disease and these agents include viruses, bacteria, fungi and protozoa. The viral envelop contains the main factor of virus effect which is called Spike (S) glycoprotein. The S protein of coronavirus infectious bronchitis virus contains 29 glycosylation sites. These help in protein folding and function of S protein. The proteomic technique used in the S protein of infectious bronchitis virus reveals 8 sites. These sites are important for the functions of infectious bronchitis virus S protein[55]. There were 101 proteins expressed in the bile sample of primary sclerosing

cholangitis patients compared with controls; the majority were intracellular and related to the ribosomal and proteasomal pathways. Another 91 proteins were identified in the bile sample of controls; most were from the extracellular space and were linked to cell adhesion, the coagulation cascade and the complement system[56]. The lipidomic communicates with proteomic to play a vital role in infectious disease. The lipid role in biological processes includes many processes such as biological host constituents of lipids and proteins and there are various lipid phosphatases, kinases, and lipases molecules are included in lipidomic technique[57]. Twelve proteins were isolated and identified from *Plasmodium falciparum* malaria. These proteins repeated the inherent parasite epitopes by fluorescence technique application[58]. The proteomic methods such as liquid chromatography-mass spectra and the matrix-assisted laser desorption/ionization with time-of-flight/time-of-flight revealed gingipains containing trypsin-like activities which help in the digestion of trefoil factor family peptides[59]. The quantitative proteomic method identified the virulence proteins and drug resistance in three clinically samples from *Escherichia coli* strains. So, the proteomic tests must be applied in the microbiological diagnostic laboratories for the determination of the drug resistant in *Escherichia coli* infection[60].

#### 4.2. Role of proteomic in human deficiency disease

The lack of necessary and vital dietary rudiments such as vitamins and minerals is the main cause of human deficiency disease. The proteomic tests and histologic examinations were applied to investigate the aggressive behavior reported in cutaneous squamous cell carcinoma (cSCC) patients. The cSCCs patients exhibited signs of ultraviolet injury, higher mutational rates, tissue damage and inflammation. The histologic analysis proved these results. The high-risk cSCCs associated with enhanced bacterial challenge. Histologic analysis revealed correlation of bacterial colonization with worse prognosis. The protein determination can serve as potential diagnostic markers and therapeutic targets in high-risk cSCCs[61]. There is efficient termination between Baf60a and Baf60c subunits of the SWI/SNF chromatin-remodeling complex as regulators of the metabolic gene programs in maintaining oxidative and glycolytic metabolism in skeletal myofibers and exercise durability, and these are responsible for impaired skeletal muscle energy metabolism which links to the pathogenesis of insulin resistance and glucose intolerance in type 2 diabetes. The transcriptional examination determines the muscle thermogenic gene program and myokine secretion as a key trigger which participates in myofiber metabolism by proving them with complete energy balance. The Baf60 deficit of skeletal muscle explains the disconnection between exercise durability and adequate metabolic homeostasis[62]. There are 315 proteins that occur in soil-transmitted helminthes [*Ancylostoma caninum*, ESPs (AcES)] by using new advance proteomic technique compared with only 105 determined previously. The greatest proteins group is the SCP/TAPs (110 of the 315 proteins) while the most rich constituents of AcES are homologues of the tissue inhibitors of metalloproteases family. There are also new groups of vaccine candidates and immunomodulatory proteins[63]. The proteomic tests were also done to study riboflavin deficiency effect on protein expression in hepatic HepG2 cells. The liquid

chromatography method connected with mass spectra (LC-MS/MS) was used to determine riboflavin deficiency. The cell viability and apoptosis results obtained confirmed that riboflavin was essential in maintaining the cytoactivity of hepatic HepG2 cells. The proteomic test identified 37 proteins were expressed following riboflavin deficiency. The observations after riboflavin deficit showed an up-regulation of the following biochemical cycles: (1) steroid catabolism, (2) apoptosis, (3) endoplasmic reticulum stress and (4) Parkinson's disease pathway while riboflavin insufficiency caused a down-regulation of many and various biochemical processes such as: (1) metabolism of fatty acid, (2) tricarboxylic citrate cycle, (3) oxidative phosphorylation and (4) metabolism of iron[64]. There are 4 proteins that were correlated with emphysema and these proteins could be summarized as follows: (1) C-reactive protein, (2) adipocyte fatty acid-binding protein, (3) leptin and (4) tissue plasminogen activator. The leptin was correlated with emphysema advance and depended on age and sex. All the above mentioned 4 proteins were correlated with body mass index after further adjustment[65]. The proteomic tests were used to identify aortic valve disease. The proteomic identified protein functions, pathways, and interaction that depended on age- and genotype-related valve stiffening. The protein variations depended on Emilin1 deficiency such as pathways, functions and biomechanical abnormalities[66]. The proteomic exhibits that biosynthetic actions in each mutant such as: (1) cell wall, (2) cell membrane phospholipids and (3) ergosterol are declined in both transcriptomal and translational levels. In the mitochondrial activities such as function, glycolysis/gluconeogenesis and ROS scavengers, the gene variations are contradictory to that of proteomic data in mutants. Consequently, the loss of energy production in mutants is compensated by increases in protein levels of glycolysis, gluconeogenesis, and anti-ROS scavengers in mutant survival[67].

#### 4.3. Role of proteomic in human genetic disease

This type of the disease is initiated by hereditary disturbances, which occurs in the human genetic map. The majority of genetic disturbances is rare and affects one person in populations or communities. Genetic disease has two major types: (1) hereditary disease from the parents' genes to fetus and (2) mutation disease caused by new mutations in the DNA. The proteomic and metabolomic tests are communicated together especially in genetic metabolic disorders. The mass spectra techniques are successes in this issue. The mass spectra is the most used method in both proteomic and metabolomic tests because of its ability to analyze a wide range of molecules, its optimal dynamic range, great sensitivity, fast determination of several molecules of metabolites in many body fluids and small samples used like dried blood spots. These techniques spare the timely diagnosis of inherited metabolic disorders, and facilitate early therapeutic application[68]. In another study, the proteomic test recorded an up-regulation of 7 proteins and these proteins are as follow: (1) C-reactive protein, (2) keratin KB40, (3) heat shock protein 27, (4) chaperonin containing T-complex protein-1, (5) T-complex protein-10, (6) keratin and (7) albumin. There is a down-regulation of another 3 proteins and these proteins are as follow: (1) apolipoprotein A1, (2) precursor phospholipase A2 and (3) phospholipase C- $\alpha$ . There is an up-regulation of 118

genes while there is a down-regulation of 28 genes from the total of 146 genes. These genes are connected with inflammation and mucin production[69]. The proteomic methods showed molecular fingerprints of complex I which had an important specialization of synaptic mitochondria. There are at least 30% of the mitochondrial enzymatic activity alterations which are related with protein richness. The molecular variances between mitochondrial sub-populations could have an influence on synaptic morphology *in-vivo*[70]. The differential expressed proteins were associated with inflammatory immune response. The protein-protein interactions test revealed new relation between vitamin D binding protein and the C677T methylene tetrahydrofolate reductase genotype and this relationship was established by a molecular genetic test[71]. The proteomic test communicated with physiological analysis showed that H<sub>2</sub>O<sub>2</sub> stress caused stressful phenotypes such as increase of *in vivo* H<sub>2</sub>O<sub>2</sub> content, decrease of photosynthetic rate, elevated osmolytes, antioxidant accumulation, and increased activities of several reactive oxygen species scavenging enzymes[72]. Alzheimer's disease causes damage of the protein synthesis in the early-stage. The oxygen exposure improved mental function and decreased mitochondrial damage in Alzheimer's disease. The increased of oxygen exposure stopped the damage in the protein synthesis and consequently the synthesis of many and various proteins involved in mRNA splicing, transcription regulation, and translation was reported. The methionine oxidation and all body oxidation levels were similar in the oxygen exposure and control group. These observations indicated that the oxygen exposure did not cause any increase in peptide oxidation levels. The oxygen exposure induced an up-regulation of many and various proteins correlated with antioxidant defense[73].

#### 4.4. Role of proteomic in human physiological disease

The physiological disease occurs when the normal human body function is affected because the human organs become malfunction. In other words, the physiological disease is abnormal human status which modifies the normal body functions leading to feelings of pain and weakness and is correlated with certain symptoms and signs. The proteomic as well as metabolomics and transcriptomic techniques were used to show the human organs with physiological application in non-alcoholic fatty liver disease in a simple screen. All these techniques help in the upcoming development of the disease biomarkers and to know the disease and evaluate the new drugs' development[74]. The immunoglobulin M antibodies phosphorylcholine induced an increase in the regulatory T cells in healthy donors, systemic lupus erythematosus (SLE) patients and atherosclerotic cells while control antibodies did not. The T cells in SLE patients caused a decrease in levels of regulatory T cells while induced an increase in Th17 cells levels compared to control. In this study, a decrease in the secretion of interleukin-17 and tumor necrosis factor- $\alpha$  was observed in SLE patients and atherosclerotic cells in immunoglobulin M antibodies phosphorylcholine. The proteomic de novo sequencing method was used and revealed that the IgM peptide was expressed in anti-PC compared to control antibodies[75]. The Kruppel-like factor 15 (KLF15) is vital in the control of adipocyte lipid cycle. Consequently, mice deficiency in KLF15 in adipose tissue showed a decline in adiposity and protected from obesity. This result related to KLF15 which controls many genes in triglycerides

synthesis and lipolytic action decreased process. So, an increase in lipid storage was observed. In conclusion, the adipose KLF15 is necessary regulator of adipocyte lipid metabolism and energy balance[76]. There is an increase in the photosynthesis-related proteins such as rubisco, plastocyanin, ATP synthase delta chain, metabolism-related proteins eIF4 and protease subunits. There is also an increase in the cytoskeleton-structure correlated proteins such as phosphatidylinositol transferring protein and profilin in the tea cultivar “Dongcha11” in low temperature and light. The Histone H4, Histone H2A.1, putative In2.1 protein and protein lin-28 homologs control the development of winter shoots and their adaptation to adverse conditions[77]. The proteomic method showed secreted exosome was found in human sweat where 1 062 proteins were detected in sweat exosome, and these proteins included 997 different proteins and 896 unique proteins compared with urine, saliva and plasma exosomes. There are various antimicrobial and immunological peptides were found in sweat exosome. So sweat exosome plays an important and major role in skin immunity. The proteomic test of sweat exosome helps in determining the exosomes physiological importance in immune homeostasis[78]. There are 245 and 379 protein groups (IDs) which were determined by the proteomic tests such as proteinPilot™ and Mascot software, respectively. There are 133 protein IDs which were identified by the peptideShaker test. Also, there is a good and established correlation between 127 proteins pathways and 349 different genes. These data are very important in characterizing the ovine circulating a cellular proteome by using liquid chromatography correlated with mass spectra. This peptide spectral data contributes to a protein library, which help in identifying huge and various proteins in ovine serum[79]. There is a major and significant decline in tyrosine nitration in the YYCFQGNQFLR peptide. This nitration occurs in the human hemopexin heme-binding site. This nitration is like rabbit and rat hemopexins nitrates. The tyrosine nitration both *in vivo* and *in vitro* models were detected by immunoblotting and selective reaction monitoring[80].

## 5. Preventive role of proteomic in human health and disease

The cathelicidins are oral peptides. These peptides are originated from defensins. Cathelicidins play vital and significant role inside the human body such as their antimicrobial, immunity, wound healing, angiogenesis and cancer control roles[81]. The new techniques such as proteomic, metabolomics, genomic and transcriptomic allow to detect and classify huge and various microorganisms in many ecosystem media such as the gastrointestinal tract, the skin, the airway system, the urogenital tract and determine all genome in these ecosystems as well as their gene products. These above mentioned tests revealed that each individual has its own ecosystem that plays a vital role in human health and disease. These techniques help to understand the pathogenesis of the human diseases. The techniques help in the diagnostic, therapeutic and preventive studies in medicine[82]. Many and various pathogens are attached by natural killer (NK) cells by immunity stimulation. The respiratory virus [Human metapneumovirus (HMPV)] is responsible for acute respiratory tract infection in children worldwide. The

HMPV infection infects 70% of children (below 5 years old) where HMPV infection could be lethal. The NKp46-receptor is a natural cytotoxic receptor in human for HMPV-infected cells. The more active NK cells are lung NK cells than blood NK cells regardless of HMPV infection[83]. The nitric oxide and superoxide-dependent S-nitrosylation of cysteine protein influence both ending proteins and the disease. The proteomic tests detected 93 proteins and 111 S-nitrosylation-modified proteins in human heart failure patients. There was an increase in phagocytes' leakage, free radical secretion and cell death while a decrease in fatty acid metabolism was recorded in human heart failure patients. The more pronounced proteins detected by proteomic analysis are: (1) ATP-synthase, (2) thrombospondin-1 and (3) vinculin where these proteins could be used as biomarkers for heart failure detection[84]. Many inflammatory diseases such as: (1) obesity, (2) impaired wound healing diabetic syndromes and (3) atherosclerosis are greatly correlated with monocyte and macrophage dysfunction. The determination of specific S-glutathionylated proteins and the mechanisms controls protein alteration in monocytes and macrophages could be help in both protective and treatment researches that focus on atherosclerosis and metabolic diseases[85]. The *SORBS1* is a human gene that plays a significant and major role in insulin signaling and this gene contains a sorbin homology domain and 3 SH3 domains in the C-terminal region. An association was observed between *SORBS1* genetic alterations and blood pressure, hypertension, and age of hypertension occurs[86]. There was a significant difference in glutathione species and metabolic status from patients with transplant surgery end-stage liver disease compared with healthy ones. The following acids play an important and vital role in hepatocellular carcinoma patients by using proteomic tests. These acids are: citric acid, myristic acid, succinic acid, *D*-threitol, *L*-methionine, pipercolic acid, fumaric acid, isoleucine, hydroxy-butyrate, glycolic, stearic and hexanoic acids. So, the glutathione species and metabolic patterns determined both liver disease severity and hepatocellular carcinoma degree in patients[87]. The septic infection, meningitis and pneumonia in both pigs and humans are caused by *Streptococcus suis* type 2. Streptococcal toxic shock syndrome exerts its effects through *virD4* gene in both pigs and humans. Streptococcal toxic shock syndrome infection, meningitis and pneumonia are decreased by 65%. The bacterial percentage in liver and brain is decreased. And lower expression of inflammatory cytokines is found by detection of *virD4* gene. So, the *virD4* gene plays an important role in streptococcal toxic shock syndrome pathogenesis through its anti-phagocytic activity and up-regulation of its expression[88]. The expression of sodium/potassium transporting ATPase interacting 2 (*NKAIN2*) genes in prostate cancer cells inhibits cancer cell progress through increasing cell apoptosis while decreasing cell movement and attack. The knockdown of *NKAIN2* increases prostate cancer cell progress by inhibiting cell apoptosis, and increasing cell movement and attack. *NKAIN2* gene resembles new tumor suppressor gene where its activity is decreased in prostate cancer. It stops the disease development and progression by inducing apoptosis and suppressing cancer cell growth, movement and attack[89]. There is a specific and important region that plays a vital and essential role in type 2 diabetes cases. This region is Cg19693031 which is located inside the 3'-untranslated region in the thioredoxin-interacting protein. So, thioredoxin-interacting protein is expressed in diabetic animals and

humans and the 3'-untranslated regions in this protein play as a key trigger in gene expression[90].

## 6. Cure role of proteomic in human health and disease

The proteomic test is used to investigate the Cisd2 protein, a key regulator of lifespan in mice and the disease gene for Wolfram syndrome 2 in humans, within the gastrocnemius after middle age among mice. The results show that, there is about 70% decrease in Cisd2 protein in gastrocnemius aging animal model. There are also a dysregulation of calcium signaling additionally, the activity of Serca1 is significantly impaired. So, Cisd2 protein is essential to the gastrocnemius muscle and it is a cure protein for muscle aging[91]. The Cdc42BPA protein and Cdc42 signaling cycle are important for colon cancer incidence. The stopping of Cdc42BPA and Cdc42 signaling decreases colon cancer cell incidence. The Cdc42BPA protein expression is increased in colon cancer tissues and up-regulated in metastatic tumors in lymph nodes. The metastasis and death of colon cancer patients depend on the Cdc42BPA protein expression. Consequently, the colon cancer incidence depends on Cdc42BPA and Cdc42 signaling and Cdc42BPA protein is used for colon cancer diagnosis and treatment[92]. The hair investigation is a key trigger in controlling many biological disturbances processes such as: (1) long term drug compliance, (2) chronic alcohol abuse and (3) forensic toxicology. The proteomic method is applied to understand human hair morphology and its use as a diagnostic tool in medicine where human hair is mostly composed of proteins[93]. The genome regulation controls both normal and diseased cases. The genome rule is controlled by chromatin remodeling complexes. This chromatin remodeling complexes are being studied by proteomic method. The proteomic test includes: (1) defining the content, (2) determining the regulation and (3) investigating the dynamics of the complexes under different cellular states[94]. The proteomic science provides significant informative data on the role of different proteins in health and disease such as inflammatory bowel disease. These studies help to understand the effects of different proteins at different periods of the disease and the different pathways that are increased or decreased at different inflammatory process periods. The proteomic explains proteins' expressions in different biochemical processes such as: (1) inflammation, (2) cellular structure, (3) endoplasmic reticulum stress and (4) energy reduction in both inflammation and treatment. Also, the role of mesenteric lymphocytes, exosomes, the intestinal mucosal barrier and the beneficial effects of some therapeutic drugs and foods components on intestinal inflammation can be achieved by controlling protein expression[95]. Forty-eight proteins were expressed in apical periodontitis compared with a healthy periodontium by applying proteomic method. Thirty proteins from total 48 proteins were expressed in all 4 lesions. The expression of heat shock protein 27 and serpin family B member 1 was double in apical periodontitis. An increase in heat shock protein 27 expression in epithelial cells was recorded while serpin family B member 1 expression was detected in neutrophils and epithelial cells[96]. The human respiratory system is highly susceptible to diseases and complications. There are many and various lung diseases such as lung cancer, tuberculosis and chronic obstructive pulmonary disease, and these diseases are the

most common causes of death worldwide.

The most public genetic disease in Caucasians is cystic fibrosis. It has many and various effects on lungs. Respiratory proteomic plays a significant role in explaining the disease mechanism, pathology of lung disease in addition to biomarker and therapeutic strategies. The proteomic test has the ability to isolate proteins from specific cellular mass. Higher protein isolation is, more protein detection is[97]. Homeostasis of cystic fibrosis trans-membrane conductance regulator (CFTR) is a dynamic process controlled by multiple proteostatic processes. The proteomic test is better method for human respiratory, cystic fibrosis epithelial cell lines and definite molecular mechanisms occurred in cystic fibrosis. There are many molecular mechanisms which regulate pathways involved with CFTR such as: (1) heat shock response, (2) cross-talk between cytoskeleton and signal transduction, (3) chronic inflammation and alteration of CFTR. These data are important in understanding of cystic fibrosis, drug treatments of cystic fibrosis in order to alleviate  $\Delta 508$ CFTR membrane instability and consequently prolong life for cystic fibrosis patients[98]. The cystathionine  $\beta$ -synthase (CBS) expression in renal tubular epithelial cells in human and rat renal tissue is inversely proportional with the fibrotic disease progress. The CBS exacerbated extracellular matrix reduced tumor growth factor- $\beta$  1-induced exacerbated extracellular matrix deposition *in vitro*. The inflammatory factors were increased in CBS reduced hexokinase-2 cells stimulated by interleukin-1  $\beta$ . The CBS is a new inhibitor in renal fibrosis and new therapeutic agent in patients with chronic kidney disease[99]. Both human gastric epithelia and mucous layers are affected by *Helicobacter pylori* (gram-negative bacteria). *Helicobacter pylori* is the main cause for chronic gastritis incidence, peptic ulceration and gastric cancer. The proteomic has an effect on various and many medical branches such as: (1) understanding the molecular basis of the infection, (2) identification of specific therapeutic drug and (3) discovery of disease biomarkers. The role of the bacterium and its most important virulence factor in the progression of gastric cells transformation and cancer is investigated by proteomic tests[100].

## 7. Conclusion

In conclusion, proteomic plays a vital and significant role in human health and disease especially in both preventive and cure studies. So, proteomic is useful and important for biomarkers development and therapeutic applications in medicine.

## Conflict of interest statement

The author declares that there is no conflict of interest.

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