ABSTRACT

Parkinson’s disease (PD) is the second most common neurodegenerative disease in the general population. Cardinal symptoms of Parkinson’s disease are resting tremor, rigidity, akinesia and bradykinesia and in advanced stages, gait impairments, postural instability and complications of chronic treatment with levodopa such as motor dysfunctions and dyskinesia. Multitude and complexity of these motor symptoms and their variability over the time have made diagnosis/assessment of them a difficult task. Moreover, the fluctuations of motor performance (ON/OFF fluctuations) in PD patients throughout their daily activities make difficult in diagnosis based their motor symptoms.

The main objective of this research is to identify the molecular biomarkers for the diagnosis of PD from peripheral blood tissue by post genomic approaches such as metallomics, metabolomics, gene expression, protein-protein interaction and systems biology. The metallomic analyses suggested, the variations in 19 elements, of which aluminium, copper, iron, manganese, phosphorus and zinc are the elements, contributes the separation of PD patients from healthy control. Moreover, aluminium is a key element involved in triggering of phosphorus, which subsequently lead to imbalance of homeostatic in PD serum. Hence, this result suggests aluminum can be the elemental marker for the diagnosis of PD. Further, FTIR spectral analysis was carried out on blood plasma in order to detect spectral parameters, which serve as biomarkers for monitoring and
identification of PD. This result suggests that bands at 1078, 1169 and 1244 cm$^{-1}$
corresponding to carbohydrates, significantly increased in all tested PD samples.
Several other spectral regions that attribute to amino acids, lipids and proteins
indicate the unique detection of PD stages. Metabolic profiling was executed in
order to determine the metabolites variations associated with FTIR spectral
variations. Such, analyses of plasma results in variation of 22 metabolites, of which
pyruvate was a major contributing metabolite for separation PD from normal.
Further, to determine the genetic basis of pyruvate variation, the protein interaction
analysis was carried out fallowed by microarray gene expression analysis, result
shows the significant down regulation of PDHB and NPFF genes in PD compared
to healthy control. Subsequently, systems biological approach was carried out to
determine the specificity of PDHB and NPFF genes in PD by comparing with 123
neurological and psychiatric disease. This result suggests that differential
expression of NPFF gene was unique to Parkinson disease representing the
possibility of biomarker, whereas PDHB gene was shown to have association not
only with PD but also with Athetosis and Friedreich Ataxia.

Furthermore, neural network was implemented on the observed
experimental values of metallomic, FTIR and metabolomic data. The results
provide an accuracy of 95, 96.29 and 97.14% in detection PD from metallomic,
FTIR, metabolomic data, respectively. In comparison of these results, metabolomic
data shown to be more effective in diagnosis of PD. However, the diagnostic
ability of all these methods are more accurate than the current available diagnosis
of PD.

In addition to the diagnostic study, molecular modeling was carried to determine the potential lead molecules for PD to avoid adverse effects of levodopa treatment. Adenosine A1 and adenosine A2A inhibitors are being considered as the adjunctive drugs to levodopa. A series of 47, 4-arylthieno [3,2-d] pyrimidine derivatives was subjected to quantitative structure-antiparkinson activity relationships (QSAR) studies to evaluate the antagonist activity towards adenosine A1 and adenosine A2A receptors. QSAR models were derived with the aid of genetic function approximation (GFA) technique using descriptors to make connections between structural parameters and antiparkinson’s activity. QSAR model was assessed using a test set of 12 compounds for A1 (r² pred = 0.961), (q² = 0.912) and 12 compounds for A2a (r² pred = 0.914), (q² = 0.781) receptor. The results revealed the significant role of DIPOLE MAG, CHI-V-3-P, WIENER, AREA, SC-2 and PHI-MAG descriptors in the antiparkinson activity of the studied compounds against adenosine A1 and adenosine A2A receptors. Subsequent, ADMET analysis shows 28 compounds can be the better candidates of drug and execution of pharmacophore model, explores the hydrogen bond donor, aromatic ring and hydrophobic groups are the key structural features for the antagonist activity.

Overall, these identified biomarkers based on post genomic approach increase the prospect of a robust molecular definition in detection of PD through the early symptomatic phase of the disease. This is an ultimate opening for
therapeutic intervention. If validated in a genuinely prospective fashion in other neurodegenerative diseases, the biomarkers trajectories described here will go a long way to facilitate the development of feasible detection and useful therapies. Moreover, implementation of neural network will be a breakthrough in clinical screening and rapid detection of PD.