eventually needed for the inhibition of adenosine receptor. A key drug target for levodopa-induced dyskinesia.

CHAPTER 6

SUMMARY AND CONTRIBUTIONS

PD is a complex neurodegenerative disorder featuring a range of physical and psychological symptoms. While primarily sporadic in nature, familial forms of PD exist. The pathogenesis of PD is not fully understood, but multiple factors and pathological processes, such as oxidative stress, mitochondrial dysfunction, excitotoxicity, neuroinflammation, and apoptosis, appear to be involved. Given the complexity of the disorder, it is perhaps unsurprising that its aetiology also appears to be complex and multifactorial in nature. A number of factors may influence PD risk including physiological, genetic, dietary/lifestyle, psychosocial, microbiological and environmental factors. Simultaneously, the diagnosis of PD is difficult because of its complex symptoms, shared with most of the movement disorders. There is no biochemical test or markers are presently available for the diagnosis of PD. The current diagnosis is based on the neurological examination and medical history. However, the accuracy of the clinical diagnosis is limited depends on the expertise of the neurologist. The focus of this research was on contributing to the diagnostic research based on the biochemical and molecular aspects of PD through an optimally designed study within the constraints of a PhD timeline and limited resources. In addition to diagnosis, a molecular modeling study was also considered, as this may be the effective in developing a new drug target for PD.
The primary objective of this research was to identify the molecular biomarkers for the diagnosis of PD from peripheral blood tissue by post genomic approaches. The goal was to use these identified markers for diagnosis and monitoring of PD patients during their early stages of disease onset. The major results and contributions of this research were:

6.1. METALLOMICS BASED DIAGNOSIS OF PD

The metallomic analyses results suggested that 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. Also, these results suggest that there is a disturbance in the elements homeostasis and inter-elements relationship in PD patients' serum. The analysis of serum elements helps in linking the underlying cellular processes such as oxidative stress, neuronal dysfunction and apoptosis, which are the dominating factors in PD. In addition, these results increase the prospect of detection of early PD from serum through neural network algorithm.

6.2. FTIR SPECTRAL BASED DIAGNOSIS OF PD

FTIR analysis was carried out on plasma in order to detect spectral parameters, which serve as biomarkers for monitoring and identification of PD. The 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 Parkinson’s disease stages.
6.3. METABOLITE BASED DIAGNOSIS OF PD

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 considered to major contributing metabolite for separation PD from normal. To determine the genetic basis of pyruvate variation, the protein interaction analysis was carried out followed by microarray gene expression analysis, result shows the significant down regulation of PDHB and NPFF gene in PD compared to healthy control. Subsequently, the systems biological approach was carried out to determine the specific dyregulation of PDHB and NPFF genes in PD compared to 123 neurological and psychiatric diseases. This result suggests that differential expression of NPFF gene was unique to Parkinson disease representing the possibility of biomarker for diagnosis, whereas PDHB gene was shown to have association not only with Parkinson’s disease but also with Athetosis and Friedreich Ataxia.

This study concludes that the application of NMR metabolite profiling of plasma fluid can provide an efficient means for detection of Parkinson's disease. the identified abnormalities in 22 circulating metabolites and gene expression bring out the scope for the molecular diagnosis of PD.

Furthermore, artificial neural network model was implemented on the observed experimental values of metallomic, FTIR and metabolomic studies. 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 these post genomic approaches are more accurate than the current available diagnosis of PD.
6.4. QSAR AND PHARMACOPHORE MODEL FOR PD TREATMENT

In addition to the diagnostic study, molecular modeling was also 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. 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.

6.5. CONCLUSIONS

Overall, our identified biomarkers based 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 in various population, 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

REFERENCES


