COMPUTATIONAL STUDIES OF SIRTUINS IN THE TREATMENT OF TYPE II DIABETES MELLITUS

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ABSTRACT

Ageing in humans refers to a biological process of life engaged with physical, psychological, and social changes. Different species of animals age at radically different paces and occurrences of diseases. Drug designing approaches related to an aging factor, Type 2 Diabetes mellitus has been reported in the present study. Resveratrol and human Sirtuins (1 to 6) are docked against Type 2 Diabetes mellitus HNF-1a motif with PDB ID: 2GYP using Hex 5.1. Resveratrol and Sirtuin 6 shown good results and can use as anti-aging drugs against Type 2 Diabetes mellitus.

Key words: Drug designing, ageing, Type 2 Diabetes mellitus, Docking.

INTRODUCTION

Ageing (British English) or aging (American English) is the accumulation of changes in an organism or object over time[1]. Ageing in humans refers to a biological and systematic process of life engaged with physical, psychological, and social changes. Various research activities presented that even late in life potential exists for physical, mental, and social growth and development[2]. Ageing is an important part of all human beings reflecting the biological changes that occur, and is also reflecting cultural and societal conventions. Indeed, aging is not an unavoidable property of life process but it is indeed the result of a genetic program[3].

In the early twentieth century, the study of aging focused primarily on biomedical models of pathology, that is, how to diagnose the diseases and chronic disabilities afflicting the elderly, and how best to treat them. It is safe to say that most of scientists studying aging prior to l980s proposed that "aging as a rising wall of mortality"[4].

Aging research crosses all areas of physiology and also relies upon biological, mathematical, and chemical tools for its study. The rapid rise of biological, biomedical and behavioral research on aging beginning in the 1970s was a response to the growing realization of both the scientific and political establishments that the American population was aging and that the Baby Boomers would reach retirement in less than 50 years, an eternity for politicians and a moment for scientists[5].

The sirtuin family of genes has been shown to have a significant effect on the lifespan of yeast and nematodes[6]. Most of the drug companies are currently searching for ways to synthesize and mimic the lifespan-extending effects of caloric restriction without having to severely reduce food consumption.

Silent information regulator (Sir) proteins, or sirtuins, are a class of proteins which possess either histone deacetylase or mono-ribosyltransferase activity and are found in organisms ranging from bacteria to humans[7,8]. Sirtuins have been concerned in the process of regulation of aging, transcription, apoptosis and stress resistance. Regulation of metabolic processes as well as cellular defense mechanisms might ultimately be the key to a possible lifespan-extending role for sirtuins in mammals. Based on previous research, mammals possess seven types of sirtuins (SIRT 1 to 7) that occupy different subcellular compartments such as the nucleus (SIRT1, -2, -6, -7), cytoplasm (SIRT1 and SIRT2) and the mitochondria (SIRT3, -4 and -5)[9]. Sirtuins may be of therapeutic utility for type II diabetes mellitus[10]. The polyphenolic compound called Resveratrol is a naturally occurring phytochemical and can be found in most of the plant species, including grapes, peanuts and various herbs and shrubs [11]. Several studies show that Resveratrol, found in red wine, can inhibit this interaction and is a putative agent for slowing down the aging process[12].

MATERIALS AND METHODS

In this work, we attempted to carry out the drug designing with the following infrastructure.

SYSTEM USED –Intel Pentium 4 GHz, 2GB RAM

OPERATING PLATFORM- Microsoft Windows XP pro 2002 service pack

SOFTWARE PACKAGES - ISIS /Draw 2.5SP4, ARGUSLAB 4.0.1, HEX 5.1

PROTEIN- 2GYP.pdb

One of the PDB Structure related to Diabetes mellitus caused due to a frustrated Schellman motif in HNF-1a with PDB id 2GYP was selected as receptor

Protein sequences related to sertuin is randomly selected from NCBI database with Accession numbers 1NP_036370(Sir1), AAD40850(Sir2), AAD40851(Sir3), NP_036372(Sir4), AAD40853 (Sir5), NP_057623 (Sir6) and NP_057622(Sir7). These sequences are submitted to Swissmodel for identification of template molecules for docking. The ligand designed on ISIS/Draw is Resveratrol, optimized by Argus and is also used for docking process.

Docking studies are done using Hex 5.1 software.

RESULTS AND DISCUSSION

Diabetes Mellitus is the most prevalent chronic disease in the world affecting nearly 25% of the population. Bioinformatics and cheminformatics are emerging fields with the potential to significantly improve the activity of drugs against diseased molecules commercially supplied to the marketplace[13].

Templates from Sir1 to Sir6 are shown in **FIGURE 1**.

Various sirtuins and Resveratrol are selected as ligands for the present study. **FIGURE 2** provides the process of designing and optimization of Resveratrol. The designed and optimized structure of Resveratrol is shown in **FIGURE 3**.

The selected receptor is displayed in **FIGURE 4**.

The distances of Ligand and Receptor have been provided in Table 1.
Resveratrol and Sirtuin 6 shown good result and can use as anti-aging drugs against Type 2 Diabetes mellitus.

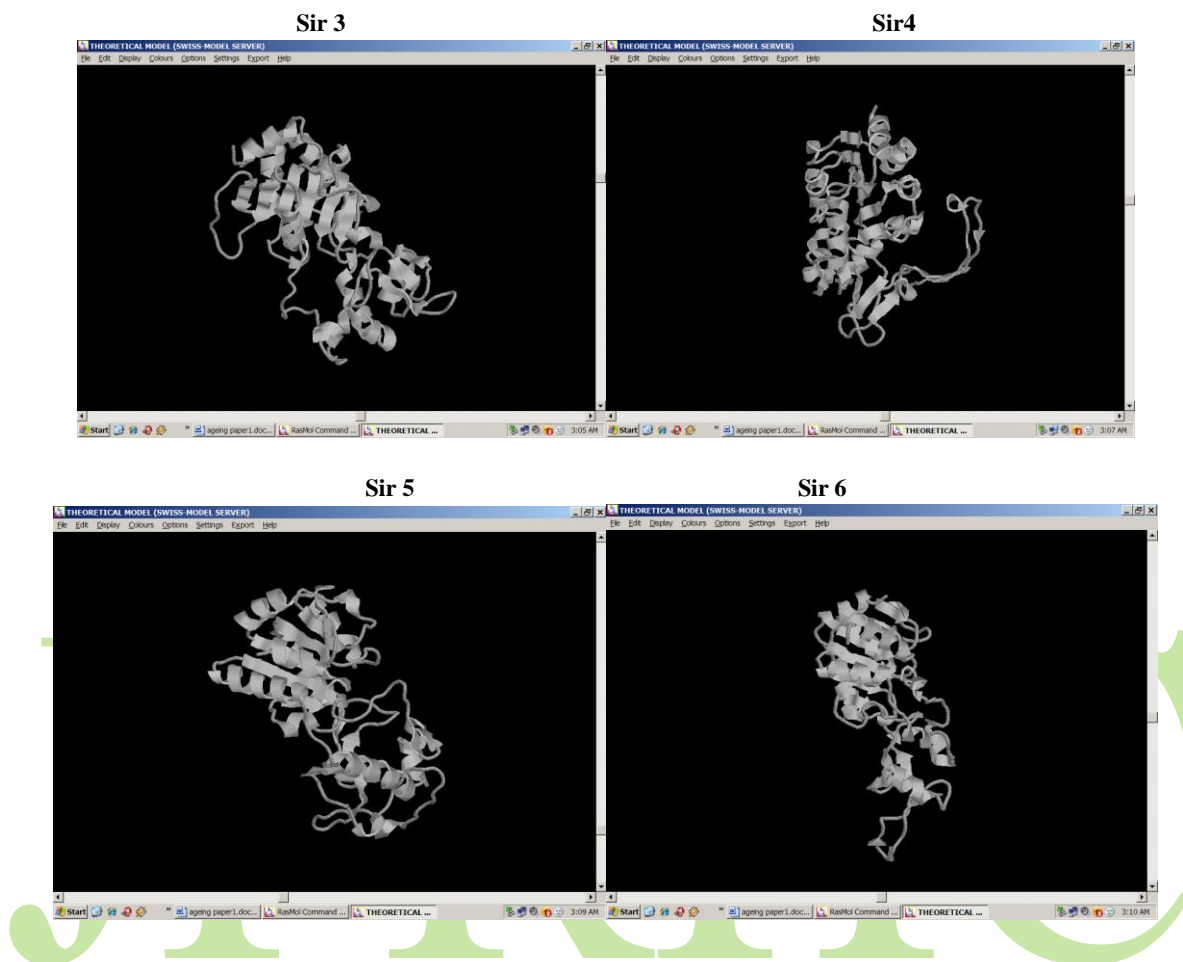**FIGURE 1: SWISSMODELED STRUCTURES OF SIRTUINS 1 TO 6 (DISPLAYED IN ARGUS)**

Sir1   Sir 2

Sir 3   **Sir4**

Sir 5   **Sir 6**
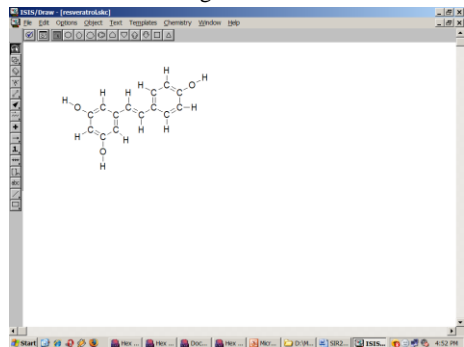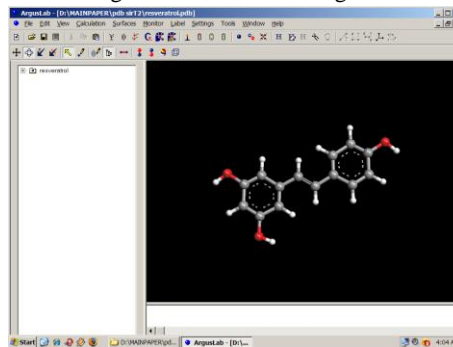

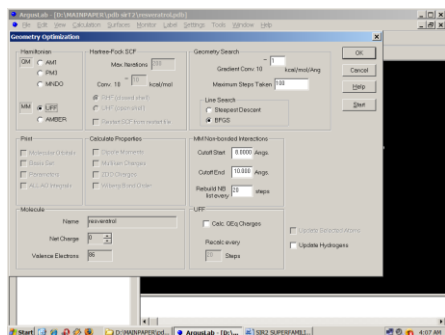**FIGURE 2: DESIGNING AND OPTIMISATION OF RESVERATROL**

A: Resveratrol Designed in ISIS /Draw   B:Designed molecule from Argus

C:Parameters selected with UFF in Argus

D:After running the designed molecule,
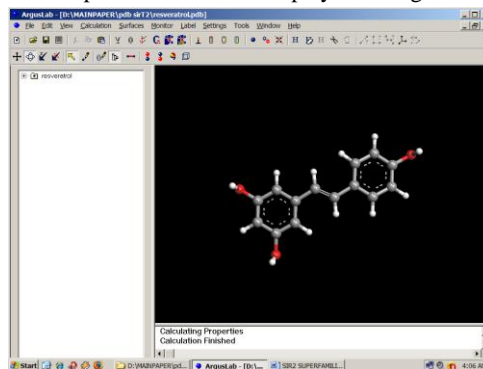the optimized structure displayed in Argus
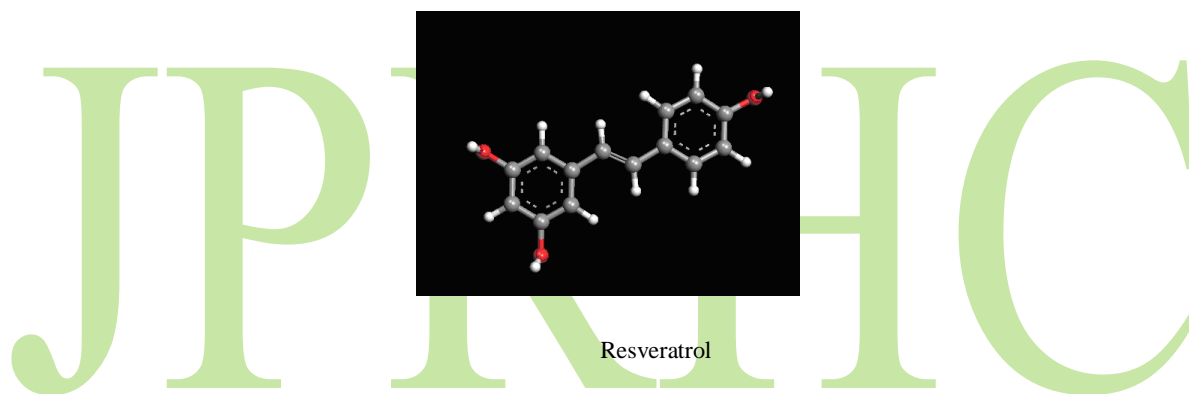
FIGURE 3: DESIGNED AND OPTIMISED DRUG

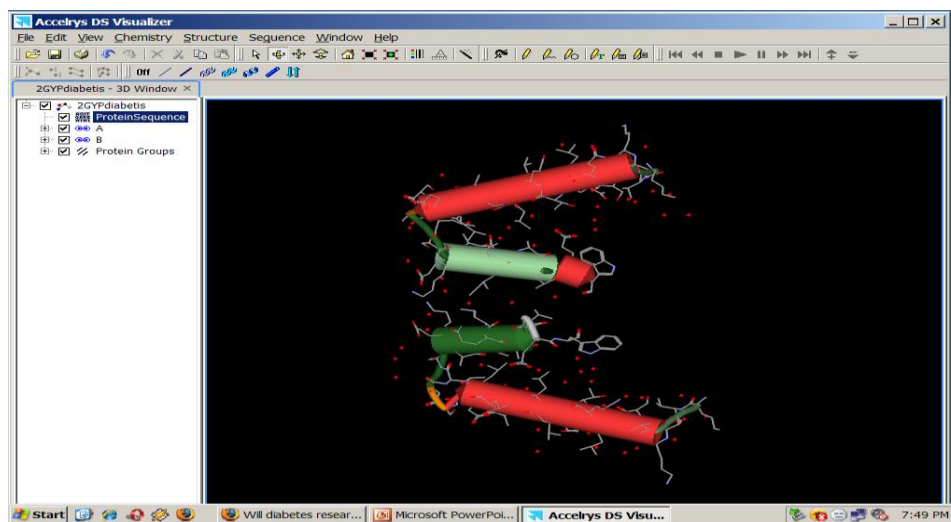Resveratrol

FIGURE 4: 2GYP.PDB MODEL FROM PROTEIN DATABANK (PDB)

TABLE 1: DISTANCE FROM LIGAND AND RECEPTOR IN ANGSTROMS

Drug/Fatty acid	2GYP(Diabetes causing molecule)
Resveratrol	3.8
Sirtuin 1	43.5
Sirtuin 2	43.9
Sirtuin 3	28.9
Sirtuin 4	43.5
Sirtuin 5	43.9
Sirtuin 6	17.6

CONCLUSION

Studies based on computational approaches can provide better results based on docking. Further studies using phytocompounds can provide cure against aging diseases such as Diabetes, Alzheimer, Parkinson, Rheumatoid Arthritis etc.

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