A DISSERTATION ON

An in-silico study of bioactive compounds from natural sources for antidiabetic potential

SUBMITTED TO THE
DEPARTMENT OF BIOENGINEERING
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DEGREE OF MASTER OF TECHNOLOGY
IN BIOINFORMATICS

BY
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M. Tech Bioinformatics (IV Semester)
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UNDER THE SUPERVISION OF

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DECLARATION FORM

I, **S Nabilah Jawed**, a student of **M.Tech. Bioinformatics** (II Year/ IV Semester) Integral University have completed my six months dissertation work entitled "**An in-silico study of bioactive compounds from natural sources for antidiabetic potential"** successfully from **Department of Bioengineering, Faculty of Engineering & Information Technology, Integral University, Lucknow** under the able guidance of **Dr. Alvina Farooqui, Professor and Head.**

I, hereby, affirm that the work has been done by me in all aspects. I have sincerely prepared this project report and the results reported in this study are genuine and authentic.

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CERTIFICATE BY SUPERVISOR

Certificate that Ms **S Nabilah Jawed** (1700101451) has carried out the research work presented in this thesis entitled **"An in-silico study of bioactive compounds from natural sources for antidiabetic potential"** for the award of **M.Tech. Bioinformatics** from Integral University, Lucknow under my supervision. The thesis embodies results of original work and studies carried out by the student himself and the contents of the thesis do not form the basis for the award of any other degree to the candidate or to anybody else from this or any other University/Institution. The dissertation was a compulsory part of her **M. Tech Bioinformatics** degree.

I wish her good luck and bright future.

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CERTIFICATE BY INTERNAL ADVISOR

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I wish her good luck and bright future.

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TO WHOM IT MAY CONCERN

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S Nabilah Jawed

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LIST OF ABBREVIATIONS

DM	Diabetes Mellitus
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
GDM	Gestational Diabetes Mellitus
CDC	Center for Disease Control and Prevention
FPG	Fasting Plasma Glucose
MTDL	Multi-Target Directed Ligand
LBDD	Ligand Based Drug Design
SBDD	Structure Based Drug Design
QSAR	Quantitative Structural Activity Relationship
IDDM	Insulin Dependent Diabetes Mellitus
GSK-3β	Glycogen Synthase Kinase- 3β
G-6-P	Glucose-6-Phosphatase
TNF	Tumor Necrosis Factor
IL-6	Interleukin-6
PPARs	Perixome Proliferator Activated Receptors
ACE	Angiotensin Converting Enzyme
ARB	Angiotensin Receptor Blocker
PDB	Protein Data Bank

1. INTRODUCTION

Diabetes is a chronic non communicable disease and a multifactorial disorder characterized by the inability of the body to produce insulin or by defects in insulin secretion and action. It is probably one of the oldest diseases known to man. About 3000 years ago, it was first reported in 1936 in Egyptian manuscript (Olokoba *et al.*, 2012). Main cause for the disease to occur is either impaired insulin secretion or lack of insulin action or both (Kerner and Brückel *et al.,* 2014). The incidence of Diabetes mellitus is on the rise all over the world (M Lehrke *et al.,* 2017). Despite decades of research in various therapies for treatment of diabetes, currently the major thrust of treatment is on insulin, secretagogues, sensitizers, alpha glucosidase inhibitors (P Malla *et al.,* 2014) . The therapeutic intervention using noninsulin medications is based on reversing the pathophysiological abnormalities that contribute to hyperglycemia (Chatterjee and Davis *et al.,* 2015).Examples of common antidiabetic drugs that promote the aforementioned effects include alpha-glucosidase inhibitors, metformin and sodium-glucose co-transporter-2 (SGLT-2) inhibitors (Bhowmick and Banu *et al.,* 2017). However, despite their prominent role in attenuating blood glucose levels, the adverse effects associated with these drugs are inevitable (LA Snook *et al.,* 2016).On the basis of aetiology and clinical presentation Diabetes mellitus is classified as Type 1 Diabetes, Type 2 Diabetes and Gestational diabetes (S Verma *et al.,* 2017).Type 1 Diabetes is caused due to autoimmune destruction of pancreatic beta cells ,body cannot fulfil the need of insulin. It is usually diagnosed in children and adolescents.(J Gromada *et al.,* 2018).It used to be called juvenile diabetes and insulin-dependent diabetes mellitus (IDDM). Since Type1 diabetes mellitus is primarily due to family member's genetic genes, a few it has been established that susceptible genes are risk factors for this form of Diabetes (T1DM) (JM Norris *et al.,* 2020). Several dietary and lifestyle variables, such as childhood obesity, rapid infant development, older maternal age and limited breastfeeding length, also contribute to the incidence of T1DM (FZ Syed *et al.,* 2022). These patients are also susceptible to other autoimmune diseases such as Grave's disease, Addison's disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anaemia, such as Hashimoto's thyroiditis (L Hao *et al.,* 2021). Non- Insulin Dependent Diabetes Mellitus (NIDDM) is another term used for Type II diabetes, characterized by hyperglycemia due to lack of insulin production or insulin action. Type II diabetes makes up about 90-95 % of cases of diabetes mellitus (R Goyal *et al.,* 2018).People with type 2 diabetes are not totally dependent on exogenous insulin but may require insulin for the control of hyperglycemias after several years (YW Tao *et al.,* 2020).Then comes Gestational diabetes which is a temporary form of diabetes in which the females are not able to produce sufficient amount of insulin during pregnancy. About 2-5% of female develop gestational diabetes (HD McIntyre et al.; 2019).The first recommended target for strategic management of gestational diabetes is the food plan (N Malaza *et al.,* 2022). According to a 2011 Center for Disease Control and Prevention (CDC) data, diabetes affects about 25.8 million

individuals in the United States (7.8 percent of the population) in 2010, with 90% to 95% of them being type 2 Diabetes mellitus (Department of Health and Human Services, Centers for Disease Control and Prevention, 2011).It is expected that in developing countries, the latter would equal or perhaps exceed the former, resulting in a twofold burden as a result of the present trend of transition from communicable to noncommunicable illnesses (Yach D *et al.,* 2004).Clinical trials also support the use of new biomarkers such as C-reactive protein, adipokines, incretins, cytokines, and others in combination, but not alone, for predicting T2DM with similar accuracy as established biomarkers(NA ElSayed *et al.,* 2023). Literature shows that the attention on the application of phytochemical constituents of medicinal plants in the pharmaceutical industry has increased significantly. For e.g.; Momordica charantia (MC) also known as bitter is an herbal medicine used as antidiabetic agent. Phenolics, alkaloids, tannins, saponins, lignin, glycosides, and terpenoids are some of the primary classes of bioactive chemicals (Weremfo *et al.,* 2023).There are various bioactive compounds from different sources, some of them are ,Cyanobacteria which are one of the most intriguing sources of new marine chemicals (R Perera *et al.,* 2023).They have anti-fungal, anti-inflammatory, anti-cancer and anti-HIV properties. Cyanobacteria produces a wide variety of toxins and other bioactive compounds, which include 40% lipopeptides which include different compounds like cytotoxic (41%), antitumor (13%), antiviral (4%), antibiotics (12%) and the remaining 18% activities include antimalarial, antimycotics, multi-drug resistance reversers, antifeedant, herbicides and immunosuppressive agents ,besides the immune effect, blue green algae improves metabolism (NS Younis *et al.,* 2022). Diabetes Mellitus is rising at alarming epidemic level throughout the world, effective drugs with low or no toxicity need to be developed. And one such way for it is the use of natural bioactive compounds which will have least side effects. From the in-silico study, it is suggested that the natural bioactive compounds of cyanobacterial strains and from other natural sources is the binding energy which determines the strength of interaction between a ligand and an enzyme. A basic assumption of any in silico study is the correctness of the input data extracted from the literature or databases (Fourches *et al.,* 2016).

AIMS AND OBJECTIVES

- Selection of diabetes markers of type 2 diabetes mellitus from existing literature.
- Screening and selection of bioactive compounds against diabetes markers through
- Lipinski's rule of 5 and ADMET Tool
- To perform molecular docking studies of selected bioactive compounds against glucose-6-phosphatase and glycogen synthase kinase-3β

REVIEW OF LITERATURE

Diabetes

The term diabetes describes a group of metabolic disorders characterized and identified by the presence of hyperglycemia in the absence of treatment (S Verma *et al.,* 2017). The heterogeneous aetio-pathology includes defects in insulin secretion, insulin action, or both, and disturbances of carbohydrate, fat and protein metabolism (Steele *et al.,* 2014). The long-term specific effects of diabetes include retinopathy, nephropathy and neuropathy, among other complications. People with diabetes are also at increased risk of other diseases including heart, peripheral arterial and cerebrovascular disease, obesity, cataracts, erectile dysfunction, and nonalcoholic fatty liver disease (Kumkrai *et al.,* 2015). They are also at increased risk of some infectious diseases, such as tuberculosis (M Lehrke *et al.,* 2017). Diabetes may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. Genital yeast infections frequently occur (AG Unnikrishnan *et al.,* 2018). The most severe clinical manifestations are ketoacidosis or a non-ketotic hyperosmolar state that may lead to dehydration, coma and, in the absence of effective treatment, death. However, in T2DM symptoms are often not severe, or may be absent, owing to the slow pace at which the hyperglycaemia is worsening (SF Farsani *et al.,* 2017).As a result, in the absence of biochemical testing, hyperglycaemia sufficient to cause pathological and functional changes may be present for a long time before a diagnosis is made, resulting in the presence of complications at diagnosis (Nabi *et al.,* 2013).It is estimated that a significant percentage of cases of diabetes (30–80%, depending on the country) are undiagnosed .Clinical risk factors and glycaemic control alone cannot predict the development of vascular complications; numerous genetic studies have demonstrated a clear genetic component to both diabetes and its complications. Diabetes has become a global epidemic as a result of global industrialization and the astonishing rise in obesity (SR Colberg *et al.,* 2016). Although it is difficult to obtain an exact assessment of prevalence due to two major factors: data collecting standards and techniques vary greatly throughout the globe; new studies forecast an increase in the prevalence of diabetes in adults from 4% in 1995 to 6.4 percent by 2025. Furthermore, it is expected to alter fast, with a 42 percent growth in rich nations from 51 to 72 million and a 170 percent increase in poor countries from 84 to 228 million. The nations most afflicted by this disease in 2025 will be India, China, and the United States. The second, and more concerning, explanation is that a sizable proportion of patients (almost half) remain unidentified even today. As a result, governments throughout the world will confront a major rise in the burden of healthcare costs, as diabetes patients are prone to both short- and long-term problems, as well as early mortality (AP Courcoulas *et al.,* 2014).

Plants from diverse families have been noted to possess potent hypoglycaemic potential.The literature revealed the substantial antidiabetic potential of many plant remedies exhibiting controlled analyses in healthy and

diseased animals as well as human in last ten years. The mode of action of these plant remedies involves the regulation of carbohydrate metabolism by restoring integrity and function of the β cells (Ostrowaski *et al.*, 2014). The one of the important method used in the treatment of type 2 diabetes is the inhibition of glycogen phosphorylase. Since production of glucose in the liver has been shown to increase in type 2 diabetes patients, so by inhibiting the release of glucose from the liver'sglycogen appears to be a valid approach (Moller *et al.*, 2001). Inhibitors which are recently used in clinical purpose are miglitol and acarbose which inhibit the activity of glucosidase such as alpha glucosidase and alpha amylase, whereas vaglibose inhibit alpha glucosidase. However, many of these antidiabetic agents have their limitations, are nonspecific, produce severe side effects and fail to reduce diabetic complications. The important side effects of these inhibitors are gastrointestinal viz., bloating abdominal discomfort, diarrhoea and flatulence (Chenget *et al.,* 2005). Therefore, there is continuous increasing failure of chemotherapeutics and increase in side effects exhibited by different chemical agents has led the need of screening several medicinal plants for their antidiabetic potential. The aqueous, hexane and methanolic extracts of Piper longam show glucose lowering effects (Nabi *et al.,* 2013). Studies conducted on the root of C. colocynthis to evaluate the biochemical parameters of alloxan-induced diabetic (AID) and normal rats after administration of aqueous, chloroform and ethanolic extracts of C. colocynthis root to observe its therapeutic effects and found the promising antidiabetic potential of the plant (Agarwal *et al.,* 2012). Ethanolic and aqueous extracts of the leaves of Bauhinia forficata, a remarkable species of this genus, have shown hypoglycaemic activity in vivo (Menezes *et al.,* 2007). Phytochemical studies on the stem aqueous extract of D. reticulata revealed numerous phenolic constituents which could have significant antidiabetic potential as shown in some other herbs (Kumkrai *et al.,* 2015). For example, it has been reported that Swartz extract containing phenolic compounds (rutin, caffeic acid, gallic acid and catechin) of Solanum torvum exhibits hypoglycemic activity and is well known for their efficiency to promote β-cell regeneration (Gandhi *et al.*, 2011). Flavonoids and triterpenoids, the two major types of compounds found in extracts of Potentilla discolour have protective effects on β-cells in diabetic rats (Lin *et al.,* 2010). Extract of Acacia nilotica acts as anti-diabetic agents by acting as sacretagouge to release insulinHypoglycemic and antidiabetic effect of Annona squamosa was reported in the leaf extract (Vardharaj *et al.,* 2011).

Risk Factors and Causes of Diabetes

The causes of diabetes are complex and only partly understood. This disease is generally considered multifactorial, involving several predisposing conditions and risk factors. In many cases genetics, habits and environment may all contribute to a person's diabetes. For example, autoimmune diabetes (type 1 and latent autoimmune diabetes of adulthood, LADA) is more common in white people, but metabolic diabetes (type 2 and gestational diabetes) is more common in people of other races and ethnicities. Type 1 is usually diagnosed

in children, but advancing age is a risk factor for type 2 and gestational diabetes. (Y Wu *et al.,* 2014). Other diabetic risk factors and causes include:

Genetics and family history: Genes also contribute to other forms of diabetes, including types 1 and 2. Family medical history is also influential to varying degrees: For example, a person whose parents both have type 1 diabetes has a 10 to 25% chance of developing that disease, according to the American Diabetes Association, and someone whose parents both have type 2 diabetes has a 50% chance of developing that disease (DT Broome *et al.,* 2021).

Weight and body type: Overweight and obesity are leading factors in type 2 diabetes and gestational diabetes. Excess fat, especially around the abdomen (central obesity), promotes insulin resistance and metabolic syndrome (J Gromada *et al.,* 2018). However, recent research indicates that obesity may hasten the development of type 1 diabetes and that the increasing rate of type 1 diabetes may be at least partly due to the rise of childhood obesity.

Sex: Though men make up less than 49% of the U.S. adult population, they account for 53% of the adult cases of diabetes, according to the National Institutes of Health (NIH). One factor may be the documented increase in recent years of low testosterone levels (male hypogonadism), which scientists have linked to insulin resistance.

Level of physical activity: Lack of regular exercise is blamed for much of the twin global epidemics of obesity and diabetes (SR Colberg *et al.,* 2016).

Diet: The effect of diet in the development of diabetes is controversial. Some studies have linked heavy consumption of soft drinks and other simple carbohydrates to risk of metabolic diabetes, and foods low in the glycemic index, such as whole grains, to reduced risk. Yet the ADA states that eating foods containing sugar does not cause the disease. The culprit, rather, is the weight gain due to sedentary habits and excess intake of calories, according to the ADA. Another dispute centers around whether being fed cow's milk early in life might be linked to type 1 diabetes (SH Ley *et al.,* 2014).

Other diseases: Medical conditions including high blood pressure, hyperlipidemia (unhealthy levels of cholesterol), polycystic ovarian syndrome, asthma and sleep apnea have been linked to type 2 diabetes. Celiac disease (gluten intolerance) and other autoimmune diseases have been linked to type 1. The many conditions that may cause secondary diabetes include pancreatitis, hemochromatosis, endocrine disorders including hyperthyroidism (Lipsky *et al.,* 2004).

Hormones: These chemical messengers can contribute to diabetes in various ways. The release of growth and sex hormones during adolescence may make some teens more susceptible to diabetes. A wide range of hormonal treatments including anabolic steroids, growth hormone, estrogens, injected contraceptives, androgen

deprivation therapy for prostate cancer and corticosteroids have been linked to secondary diabetes (Mokabberi and Ravakhah *et al.,* 2007).

Medical treatments: In addition to hormonal therapies, medications including diuretics, beta blockers (another class of antihypertensives), immunosuppressives, antiretrovirals (AIDS/HIV drugs) antipsychotics, lithium, and some antidepressants, anticonvulsants and chemotherapy drugs have been linked to an increased risk of secondary diabetes. Pancreatectomy and radiation therapy may also result in secondary diabetes (AP Courcoulas *et al*., 2014).

Other chemicals: Common consumer plastics and plastics ingredients including phthalates and bisphenol A have also been linked to insulin resistance in some cases. Exposure to agricultural pesticides during pregnancy has been tentatively linked to gestational diabetes (J Gromada *et al.,* 2018).

Environmental factors: Smoke, air pollution and even genetics contribute to the formation of free radicals (T Dendup *et al.,* 2018). When these radicals build up, they can destroy cells, including those involved in the production of insulin. Cold weather is another possible environmental factor in type 1 diabetes. This disease occurs more commonly in cold climates and develops more frequently in the winter than the summer (H Haller *et al.,* 2017).

Smoking: Cigarette smoking is a risk factor for type 2 diabetes and possibly other forms of diabetes (J Maddatu *et al.,* 2017).

Alcohol: Excessive use of alcohol is a risk factor for diabetes. For example, it can cause pancreatitis. However, some research has found that light drinking may decrease the risk of becoming diabetic (JCN Chan *et al.,* 2009).

Classification of Diabetes

Hyperglycaemia is the defining common feature of all types of diabetes, but aetiology, underlying pathogenic mechanisms, natural history and treatment for the different types of diabetes differ. Ideally, all types of diabetes would be defined by defining features that are specific and exclusive to that type of diabetes (3). However, some types of diabetes are difficult to classify (ABH Widatalla *et al.,* 2009).

Classification systems can broadly be used for three primary aims:

1) Guide clinical care decisions

2)Stimulate research into aetio-pathology

3)Provide a basis for epidemiological studies

4)Clinical care decisions

Subtyping diabetes is important in clinical care for diagnosis, to guide treatment choices, and when making treatment decisions for a person whose glycaemic control is unsatisfactory. An incorrect treatment decision could risk a person developing diabetic ketoacidosis (DKA) or lead to unnecessary insulin therapy in the case of some forms of monogenic diabetes. The phenotype of both T1DM (overweight or obese) and T2DM (younger, normal weight) have changed over time and contributes to clinicians' increasing difficulty classifying types of diabetes.

Aetio-pathology:The aetiology and pathogenesis of diabetes can be described simplistically as problems with insulin sensitivity and insulin secretion, but the underlying specific defects are complex and not well understood (World Health Organization,2019). While some specific defects have been identified (e.g. genetic abnormalities resulting in insulin secretory problems), identifying these abnormalities will improve our understanding of the underlying mechanisms of diabetes and its treatment, but at present, our limited knowledge of these complex abnormalities hinders the development of a practical and clinically useful classification system for diabetes (J Reed *et al.* ,2021).

Epidemiological Studies:Most epidemiological studies report overall prevalence of diabetes without distinguishing between subtypes, despite the value of subtyping for such studies. Subtyping T1DM and T2DM in population studies is feasible using frequently available clinical information. Some studies have reported the population prevalence of other forms of diabetes, e.g. monogenic diabetes and diabetes due to pancreatic disease(AT Hattersley and KA Patel *et al.,* 2017) . Although the majority of diabetes patients fit into the two main etiopathogenetic categories of type 1 and type 2 DM, this rigorous classification is not appropriate in certain individuals (M Monteiro *et al*., 2023). The categorization is frequently based on the clinical presentation upon diagnosis, and it is usual clinical practice to classify patients based on the factors listed below:

1. Diabetes onset age
2. Hyperglycemia onset abruptness
3. The existence of ketosis during the presentation
4. Obesity degree
5. The requirement for insulin at the time of diagnosis.

Type 1 Diabetes Mellitus

Type I diabetes is insulin dependent immune mediated or juvenile onset diabetes caused due to lack of functional beta cells which are unable to produce sufficient insulin (Cooke and Plotnick et al., 2008) or when insulin producing cells are being attacked by body's defense system as a result of auto immune reaction. People of any as can be affected by the disease, but most commonly children or young adults are affected. Therefore, patients suffering from Type I are totally dependent on exogenous source of insulin every day to control the glucose level in their body. To survive, patients must administer insulin medication regularly. Sometimes patients with autoimmune diabetes develop insulin resistance because of weight gain or genetic factors. This condition is known as double diabetes. The subsequent lack of insulin leads to elevated blood and urine glucose. Patients with Type I diabetes are solely dependent on exogenous insulin for survival. Type 1 diabetes used to be called juvenile diabetes and insulin-dependent diabetes mellitus (IDDM) (FZ Syed *et al.*,2022).

Contributing factors of type 1 diabetes mellitus is primarily due to family member's genetic genes, a few it has been established that susceptible genes are risk factors for this form of Diabetes (T1DM) This involves some of the forms of human leukocyte antigen (HLA) (CJ Garey *et al.*,2022). Environmental factors, such as viral infections, low vitamin D levels and lower exposure to ultraviolet rays, may also cause T1DM.Several dietary and lifestyle variables, such as childhood obesity, rapid infant development, older maternal age and limited breastfeeding length, also contribute to the incidence of T1DM (I Zucker *et al.*,2022).

Type 1 diabetes symptoms can appear suddenly and may include feeling more thirsty than usual, urinating a lot,bed-wetting in children who have never wet the bed during the night,feeling very hungry,losing weight without trying,feeling irritable or having other mood changes, feeling tired and weak and having blurry vision. Over time, type 1 diabetes complications can affect major organs in the body. These organs include the heart, blood vessels, nerves, eyes and kidneys. Having a normal blood sugar level can lower the risk of many complications (BC Kwon *et al*.,2022)

Genetically engineered human insulins have improved care of type 1 diabetes, and devices for continuous glucose monitoring may revolutionise care. An interplay between genetic susceptibility and environmental factors (triggering or suppressive) may account for the pathogenesis of type 1 diabetes. Many associations with various environmental triggers have been found in type 1 diabetes, but so far only congenital rubella syndrome has been conclusively associated with the disease. The expression of diabetes related autoantibodies in young children monitored from birth indicates that these markers are a major risk factor for the future development of type 1 diabetes. To date no treatment has been shown to prevent type 1 diabetes in humans. More than 100 different treatments prevent type 1 diabetes in the NOD mouse model, and this may indicate that disease prevention in this model is "too" easy. Two major trials have been conducted to try to prevent type 1 diabetes.

In the United States, the diabetes prevention trial (DPT-1) was started in 1994 with the aim of determining whether antigen-based treatment with insulin (oral and parenteral insulin treatment in relatives at high and moderate risk) would prevent or delay diabetes. These treatments did not overall slow the progression to diabetes. The European nicotinamide diabetes intervention trial (ENDIT) also found no difference in protection from diabetes when participants were assigned to either oral nicotinamide or placebo treatment (D Devendra *et al.*,2004). No treatment has been shown to safely prevent type 1 diabetes in humans, although islet transplantation and new immunosuppressive regimens show that the disease can be cured. Insulin remains the main treatment in type 1 diabetes. The diabetes control and complications trial (DCCT) showed the importance of strict metabolic control in delaying and preventing complications. The risk of hypoglycemia is still the major limiting factor in achieving euglycemia with insulin treatment. The introduction of rapidly absorbed insulin analogues has reduced variability of insulin absorption and allows insulin administration in young children after meals. Another recent introduction to the insulin market has been insulin glargine, which functions as a very long acting insulin (peak less basal insulin). The use of metformin treatment alongside insulin has increased in patients with type 1 diabetes. Recent studies have suggested that metformin might benefit type 1 diabetes patients who are overweight, are receiving large doses of insulin, or have an HbA1c > 8%.32 The coexistence of insulin resistance in patients with type 1 diabetes is a new area of interest. Islet transplantation with modified immunosuppressive regimens can cure type 1 diabetes. Islet transplantation is a consideration for the limited but important subset of patients with recurrent severe hypoglycemic episodes not responsive to medical management (FZ Syed *et al.*, 2022).

Type 2 Diabetes Mellitus

Type 2 Diabetes mellitus is an illness associated with the pancreas and the individual affected by this illness cannot regulate their blood sugar via the secretion of insulin a vital hormone in the regulation of blood sugar. Type 2 Diabetes is generally associated with a decreased life expectancy of ten years. Diabetes Mellitus Type 2 is dominantly characterized by high insulin levels and insulin resistance in relation to insulin deficiency. For example, the normal range for the insulin levels of a non diabetic individual are 60 to 100 mg and 140 mg or less after meals or snacks while the insulin levels of diabetic individuals differ in range, but are normally higher than 140 mg. Many with T2DM have relative insulin deficiency and early in the disease absolute insulin levels increase with resistance to the action of insulin . Most people with T2DM are overweight or obese, which either causes or aggravates insulin resistance. Many of those who are not obese by BMI criteria have a higher proportion of body fat distributed predominantly in the abdominal region, indicating visceral adiposity compared to people without diabetes. However, in some populations, such as Asians, β-cell dysfunction appears to be a more notable prominent than in populations of European descent . This is also observed in thinner people from low- and middle-income countries such as India , and among people of Indian descent living in high-

income countries. In addition, the response to oral blood glucose medications is often poor among young people with diabetes. Contibuting factors of Type 2 Diabetes Melllitus:

1)The development of Type 2 Diabetes is generally promoted by multiple factors such as an inadequate diet and lack of physical activity which directly correlates with obesity which is perceived as the primary contributor for the majority of patients diagnosed with Type 2 Diabetes. Many of the factors that contribute to Type 2 Diabetes are generally associated with the metabolism of an individual. There are also numerous genetic elements that increase an individuals risk of developing Type 2 Diabetes such as Donohue Syndrome a severe and rare genetic disorder that ravages the affected individual's insulin receptors, but other medical conditions (i.e. Hyperthyroidism) can also promote this illness in various individuals(R Hariharan *et al*., 2022).

Symptoms of Type 2 Diabetes Mellitus are Polyuria (frequent urination), Polyphagia (increased appetite), Polydipsia (increased thirst), and weight loss.Many individuals may not be aware of any symptoms until they are diagnosed by a healthcare professional.Changes in the prevalence of the symptoms of depression, lonliness and insomnia were detected during the Covid 19 pandemic(AM Chao *et al.,* 2022).

Gestational Diabetes

Gestational diabetes mellitus (GDM) is described as varying degrees of glucose intolerance discovered throughout pregnancy. GDM is identified by screening pregnant women for clinical risk indicators and testing for impaired glucose tolerance, which is typically, but not always, moderate and asymptomatic. GDM appears to be caused by the same wide range of physiological and genetic problems that define diabetes in general. When they are not pregnant, women with GDM are at a significant risk of acquiring diabetes. Thus, GDM offers a unique chance to research the early pathophysiology of diabetes and create diabetes prevention strategies (N Malaza *et al.,* 2022). GDM is clinically detected to identify pregnancies at high risk of perinatal morbidity and death. The data available do not define a threshold of maternal glycemia at which such risk begins or rapidly increases (CA Crowther *et al*., 2022). Until far, understanding the mechanisms behind poor glucose control in GDM has had little influence on therapeutic therapy during pregnancy.Fasting glucose measurements in the early postpartum period will identify women with diabetic-like persistent fasting hyperglycemia. Other women should undergo an OGTT within the first 2-6 months postpartum and, if not diabetic, yearly diabetes testing(C Eberle *et al*., 2022). Women having a history of GDM were included in at least two trials of diabetes prevention in high-risk adults. In the US Diabetes Prevention Program (DPP), intense lifestyle changes to promote weight loss and improve physical activity reduced the incidence of type 2 diabetes by 58 percent in persons with impaired glucose tolerance. GDM was one of the risk variables that contributed to the study's inclusion. (ABH Widatalla *et al.,* 2009). Diabetes protection was reported in all ethnic groups. Metformin treatment lowered the

incidence of diabetes in the same trial, albeit to a smaller extent and especially in the youngest and most overweight subjects. Specific findings from women with a history of GDM have yet to be reported (A Sweeting *et al*., 2022).

Symptoms Of Diabetes

The signs and symptoms of diabetes are disregarded by many because of the chronic progression of the disease. People do not consider this as a serious problem because unlike many other diseases the consequences of hyperglycaemia are not manifested immediately. People are not aware that damage can start several years before symptoms become noticeable. This is unfortunate because recognition of early symptoms can help to get the disease under control immediately and to prevent vascular complications. The classic symptoms of untreated diabetes are weight loss, polyuria (increased urination), polydipsia (increased thirst) and polyphagia (increased hunger),depression (Magdalena Beran *et al*., 2021).In addition they also include blurry vision, Headache, Fatigue , slow healing of cuts and itchy skin (Laura Soldevila-Boixader *et al.*, 2023).Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes.A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadromes (AG Mersha *et al*., 2022)

Complications Of Diabetes

All forms of diabetes increase the risk of long-term complications. These typically develop after many years (10–20). The major long-term complications relate to damage to blood vessels. Diabetes doubles the risk of cardiovascular disease. About 75% of deaths in diabetics are due to coronary artery disease (Magdalena Beran *et al*., 2021). Other include “macrovascular" diseases (stroke), peripheral vascular disease. The primary complications of diabetes is due to damage in small blood vessels which includes damage to the eyes, kidneys, and nerves. Damage to the eyes is known as diabetic retinopathy, is caused by damage to the blood vessels in the retina of the eye, and can result in gradual vision loss and blindness. Damage to the kidneys, known as diabetic nephropathy, can lead to tissue scarring, urine protein loss, and eventually chronic kidney disease, sometimes requiring dialysis or kidney transplant. Damage to the nerves of the body, known as diabetic neuropathy, is the most common complication of diabetes (AG Mersha *et al*., 2022). The symptoms can include numbness, tingling, pain, and altered pain sensation, which can lead to damage to the skin. Diabetes-related foot problems (such as diabetic foot ulcers) may occur, and can be difficult to treat, occasionally requiring amputation. Additionally, proximal diabetic neuropathy causes painful muscle wasting and weakness known as Diabetic Amyotrophy (Dunya *et al.*, 2022).

Diagnosis Of Diabetes

Diabetes screening and diagnosis tests are widely available. The screening test is the same as the diagnostic test, so a positive screen is equivalent to a diagnosis of pre-diabetes or diabetes. Although approximately 25% of patients with type 2 DM have microvascular complications at the time of diagnosis, indicating that they have had the disease for more than 5 years (*Dunya et al., 2022)*.It is still based on the American Diabetic Association (ADA) guidelines from 1997 or the World Health Organization (WHO) National Diabetic Group criteria from 2006, which are for a single raised glucose reading with symptoms (polyuria, polydipsia, polyphagia, and weight loss), otherwise raised values on two occasions, of either fasting plasma glucose (FPG) 7.0 mmol/L (126 mg/dL) or an oral glucose tolerance test (OGTT), two hours after the FPG is the focus of the 1997 ADA recommendations for diabetes diagnosis, whereas the OGTT is the focus of the WHO (Cox *et al.,* 2009). Glycated haemoglobin (HbA1c) and fructosamine are also useful for tracking blood sugar control over time. However, in addition to the recommended measures, practising physicians frequently use other measures. The International Expert Committee (IEC) recommended the additional diagnostic criteria of a HbA1c result of 6.5 percent for diabetes in July 2009. The committee proposed that the term "pre-diabetes" be phased out, but identified a range of HbA1c levels between 6.0 and 6.5 percent to identify those at high risk of developing DM. As with glucose-based tests, there is no definite HbA1c threshold at which normalcy ends and diabetes begins. The IEC chose to recommend a cut-off point for DM diagnosis that emphasises specificity, stating that this balanced the stigma and cost of incorrectly diagnosing individuals as diabetic against the minimal clinical consequences of delaying the diagnosis in a patient with a HbA1c level of 6.5 percent *(*International Expert Committee *et al.,* 2009).

Bioactive Compounds

The word ‘bio’ is derived from the Greek “Bios” which means refers to life while active is obtained from the latin meaning ‘full of energy’.Bioactive compounds refers to extra nutritional constituents present in small quantities in food.Bioactive substances are also known as nutraceuticals, a word coined by Stephan DeFelice in 1979 that refers to their presence in the human diet as well as their biological activity.Bioactive chemicals found as natural elements in food give health advantages in addition to the product's fundamental nutritional value.The substances that have received the greatest attention are antioxidants, which have been shown to reduce the risk of chronic illnesses such as cancer and cardiovasculardisease.

Table 1. Showing the list of bioactive compounds

S. No	Compounds	Class	Sources	Activity	Reference
1	Apigenin	Flavanone	Parsley,Celery,Rosemary,Oregano,Thyme, Basil	1.Activation of ERK1/2 2.Attenuates the production of proinflammatory cytokines	R Ginwala *et al.,* 2019
2	Diosmin	Flavanone	Lemon ,Orange,Buddha Fingers	1. Activation of ERK 1/2	GR Gandhi *et al*.,2020
3	Quercetin	Flavanone	Capers,Onions,Cranberries,Blueberries	1-Inhibition of NF-κB system 2. Reduction in serum level of both TNF-α and CRP	S Vishwas *et al*.,2023Aljelehawy *et al*.,2022)
4	Kaempferol	Flavanone	Tomatoes,Green,Tea,Potatoes,Broccoli,Brussels,Sprouts	1. AMPK activation 2. Decrease the fasting blood glucose, and improved insulin resistance	MM Zari *et al*.,2023 SC Mohan *et al*.,2021
5	Eriodictyol	Flavanone	Grapefruits,Oranges,Tomatoes,	1. Suppress the activation of NF-κB system	A Islam *et al*.,2020
6	Hesperetin	Flavanone	Lemon,Orange,Peppermint,Tangerine	1. Suppress the activation of NF-κB system 2.Downregulation of pro-	YJ Chen *et al*.,2019

				inflammatory cytokines and oxidative stress markers	X Zhu *et al*.,2021
7	Baicalein	Flavanone	Parsley,Cellery,Capsicum,Pepper	1.Activation of AMPKpathways 2.Supress fatty acid synthesis,gluconeogensis and increases themitochondrial β-oxidation	C Zhu *et al*.,2020
8	Chrysin	Flavanone	Skullcap,Honey	1. Supression of TNF-α production and activation of NF-κB activation	T Farkhondeh et al.,2019
9	Catechin	Flavanol	Green Tea,Chocolate,Beans,Cherry	1.Supress the activation of NF-κB system through the inhibition of pro-inflammatory cytokines production	L Wen et al.,2022 T Orita et al.,2023
10	Genistein	Isoflavanoid	Soy flour,Soy milk,Soy beans	1.Represses the release of TNF-α production 2.Inhibits the activation of ERK and P38 phosphorylation	HN Chu *et al*.,2021 S Patra *et al*.,2023
11	Resveratrol	Stillbene	Grapes,Wine,Peanut,Cocoa berries	1.Suppress the activation of NF-	YJ Song *et al*.,2020

				κB signalling pathway 2.Downregulates the COX-2 gene expression which increase the release of pro-inflammatory mediators	KX Li *et al.*,2021
12	Emodin	Stillbene	Rhubarb Buckthorn	1.Suppress the activation of NF-κB system 2.Down-modulated the adhesion molecules	C Chen *et al.*, 2022 L Lu *et al.*, 2022

Bioactive compounds from marine source

Nature has contributed significantly to medication development for humans since the dawn of time by offering curative remedies. The marine biotope, which covers about threequarters of the earth's surface, is one of nature's riches. Polyphenolic compounds are among the interesting antioxidant compounds isolated previously from marine resources, including micro- and macroalgae. In general, phenolic compounds are divided into ten types, based on their structure. These ten groups are: simple phenols, phenolic acids, hydroxycinnamic acids, coumarins, naphtoquinones, xanthones, stilbenes, anthraquinones, fl avonoids, and lignins. Marine red algae, such as P. cruentum, and cyanobacteria, like A. platensis ,can produce up to 8% in phycobiliproteins, which are already used as fluorescent markers when linked covalently to antibodies, A-protein, biotin, lectins, hormones (Perez-Garcia et al.;2011). Phycobiliproteins are composed by a protein and a chromophore part (linked by covalent bonds) called phycobilin. Phycocyanin from Arthrospira and phycoerythrin from Porphyridium are two of the most known phycobiliproteins. They can be applied in immunity assays, based on fluorescency, and in microscopy and DNA assays, as nonradioactive markers. Tauramamide is a new lipopeptide antibiotic that contains two D amino acids and is acylated at the N-terminus. Both structural features are hallmarks of non-ribosomal peptide synthase biosynthetic origin (Desjardine et al., 2007). A marinederived Penicillium sp. PSU-F44 was isolated from the same sea fan species (Annella sp.). Fungi of the genus Penicillium are known to

produce a large variety of compounds with a wide range of biological and pharmacological activities. Dolastatin 10 (Dol-10), a leading marine pentapeptide isolated from the Indian Ocean mollusk Dolabella auricularia, contains three unique amino acid residues. Dol-10 can effectively induce apoptosis of lung cancer cells and other tumor cells at nanomolar concentration, and it has been developed into commercial drugs for treating some specific lymphomas, so it has received wide attention in recent years. Pharmacological studies of bryostatin-1 have mainly been focused on its action in preventing tumor growth. (F Xu et al.; 2019).

Table 2. Showing the List of Bioactive Compounds from Marine Sources

S. No	Compounds	Class	Sources	Activity	Reference
1	Colchicine	Phenolic acid	Saffron,Colchicium	1.Mitigates inflammatory cell infiltration 2.Suppression of MCP-1 and ICAM-1 expression	M Kuzemczak *et al*.,2021 CC Chu *et al*.; 2022
2	Resveratrol	Stillbene	Grapes,Wine, Peanut,cocoa ,berries	1.Suppress the activation of NF-κB signaling pathway 2.Downregulates the COX-2 gene expression which increase the release of pro-inflammatory mediators	YJ Song *et al*.;2020 KX Li *et al*.;2021

3	Emodin	Stilbene	Rhubarb ,Buckthorn	1.Suppress the activation of NF-κB system	C Chen et al.; 2022
4	Asperversiamides B,C,F,G (10-13)	Alkaloids	A.versicolor	Anti-inflammatory	J Xu *et al.*,2019
5	Luteoride E(14)	Alkaloids	A. terreus	NA	Y Hu *et al.,* 2021 K Amr *et al.,* 2023
6	1R,6R,7R,10S-10-hydroxy-4(5)cadinen-3-one (30)	Terpenoids	Hypocreales sp. HLS-104	against NO with Emax values of 10.22% at 1 μM in LPS-activated RAW264.7 cells	H Zhu *et al.,* 2013
7	Mangicols A and B (31, 32)	Terpenoids	F. heterosporum CNC-477	81% and 57% inhibition rate at 50 μg per ear in PMAinduced mouse ear edema assay	S Chen *et al.*,2022
8	Chondroterpenes A, B, H (33–35) Hirsutanol A (36) Chondrosterins A, B (37, 38)	Terpenoids	Chondrostereum sp. NTOU4196	against NO with considerable inhibitory effects at 20 μM in LPS-activated BV-2 cells	J Xu *et al.,* 2019
9	Lovastatin (39)	Terpenoids	A. terreus	against NO with IC50 value of 17.45 μM in LPS-activated RAW264.7 cells	S Gentie *et al.*,2019
10	Aspertetranones A−D (40−43)	Terpenoids	Aspergillus sp. ZL0-1b14	against IL-6 with 43% and 69% inhibition rates at 40 μM in LPS activated RAW264.7 cells	AMS Mayer *et al.,* 2019
11	Pleosporallins A−C (44−46)	Terpenoids	Phoma sp. NTOU4195	against IL-6 with about 30.0% inhibition rate at5–20 μg/mL in LPS	J Xu *et al.,* 2019

				activated RAW264.7 cells	
12	acetoxydehydroaustin ol , Austinolide (48) acetoxydehydroaustin , hydroxyisoaustinone (50) 11 acetoxy isoaustinone (51)	Terpenoids	Penicillium sp. SF-5497	against NO with IC50 values of 61.0, 30.1, 58.3, 37.6, and 40.2 μM in LPS-activated BV-2 cells	in-Soo Park *et al.*,2018
13	Citreohybridonol (52)	Terpenoids	Penicillium sp. SF-5497	antineuroinflammatory activity	FC Özkaya *et al.*, 2018
14	Tanzawaic acid Q (53) Tanzawaic acids A (54), Terpenoids C (55), D (56), and K (57)	Terpenoids	P. steckii 108YD142	against NO with considerably anti inflamematory activity in LPS-activated RAW264.7 cells	HJ Shin *et al.*, 2015
15	2E,4Z-tanzawaic acid D (58) Tanzawaicacids A (54), E (59)	Terpenoids	P. steckii 108YD142	against NO with IC50 values of 37.8, 7.1, and 42.5 μM in LPS active-ated RAW264.7 cells	TH Quang *et al.*, 2014
16	Stachybotrysin C (60), Stachybonoid F (61) ,Stachybotylactone(62)	Terpenoids	P. steckii 108YD142	against NO with IC50 values of 27.2, 52.5, and 17.9 μM in LPS activetedRAW264.7cells	P Zhang *et al.*, 2017
17	Versicolactone G (63) Territrem A (64)	Polyketides	A. terreus	against NO with IC50 values of 15.72 and 29.34 μM in LPS active ated RAW264.7 cells	Liu *et al.*, 2018
18	Eurobenzophenone B (65) Canthone A (66) 3-de-O-	Polyketides	A. europaeus WZXY-SX-4-1	against NF-κB with significant inhibition in LPS-activated	Du *et al.*, 2018

19	Violaceol II (71)Cordyol (72)	Polyketides	A. sydowii 05B-7F-4	against NO with weak inhibition in LPS active ted RAW264.7 cell	S Liu *et al.,* 2017
20	TMC-256C1 (73)	Polyketides	Aspergillus sp. SF-6354	against COX-2 with IC50 values of 11.1, 4.2, and 6.4 μM in LPS-activated RAW264.7 cells	DC Kim *et al.,* 2016
21	Aurasperone F (74) Aurasperone C (75) Asperpyrone A (76)	Polyketides	A. niger SCSIO Jcsw6F30	against COX-2 with IC50 values of 11.1, 4.2, and 6.4 μM in LPS-activated RAW264.7 cells	W Fang *et al.,* 2016
22	Diorcinol (77) Cordyol C (78) 3,7dihydroxy-1,9-Dimethyldibenzofuran (79)	Polyketides	Aspergillus sp. SCSIO Ind09F01	against the COX-2 expression with IC50 values of 2.4−10.6 μM	R Orfali *et al.,* 2021
23	Cladosporin 8-O-αribofuranoside,Cladosporin, Asperentin 6-O-methylether Cladosporin 8-Omethyl ether 4 0 -	Polyketides	Aspergillus sp. SF-5974 and Aspergillus sp. SF-5976	against NO and PGE2 with IC50 values of 20 −65 μM in LPS-activated microglial cells	Kim DC *et al.,* 2015
24	Asperlin (86)	Polyketides	Aspergillus sp. SF-5044	against NO and PGE2 in LPS-activated murine macrophages	J Xu *et al.,* 2019
25	Guaiadiol A (87)4,10 ,11trihydroxyguaiane (88)	Polyketides	P. thomii KMM 4667	against NO with 24.1% and 36.6% inhibition at 10.0 μM in LPSactivated murine macrophages	J Xu *et al.,* 2019 AR Carroll *et al.,* 2019
26	P. thomii KMM 4667	Polyketides	Penicillium sp. SF-5629	against NO with IC50 values of 8.1 and 8.0 μM in LPS-activated	AMS Mayer *et al.,* 2019

				BV2 cells	
27	Penicillium sp. SF-5629	Polyketides	Penicillium sp. SF-5629	against NO and PGE2 with IC50 values of 21.9–27.6 µM in LPS-activated RAW264.7 and BV2 cells	NTT Ngan *et al.*, 2017
28	Penicillinolide A (91)	Polyketides	Penicillium sp. SF-5292	against NO, PGE2, TNF -α, IL-1β and IL6 with IC50 values of 20.47, 17.54, 8.63, 11.32, and 20.92 µM in LPS-activated RAW264.7 and BV2 cells	F Almasi *et al.*, 2021
29	Penstyrylpyrone (92)	Polyketides	Penicillium sp. JF-55	against NO and PGE2 with IC50 values of 1.9–18.1, and 2.8–18.7 µM in LPS-	M Nazir *et al.*, 2021
30	Curvularin,(11R,15S)-11 hydroxycurvularin,(11S,15S)-11hydroxycurvularin (11R,15S) 11methoxycurvularin (11S,15S) 11methoxycurvularin (10E,15S)-10,11dehydro curvularin(10Z,15S)-10,11dehydrocurvularin	Polyketides	Penicillium sp. SF-5859	against NO and PGE2 with IC50 values of 1.9–18.1, and 2.8–18.7 µM in LPS-activated RAW264.7 cells	HN Wang *et al.*, 2022
31	Pyrenocine A (100)	Polyketides	P. paxilli	against TNF-α and PGE2 in LPS-activated macro phages	TR Toledo *et al.*, 2014
32	Asperflavin (101)	Polyketides	E. amstelodami	against NO and PGE2 with 4.6% and 55.9% inhibition rates to NO and PGE2 at 200 µM in LPS-activated RAW264.7 cells	J Xu *et al.*,2019

33	Questinol (102)	Polyketides	E. amstelodami	against NO and PGE2 with 73.0% and 43.5% inhibition rates at 200 µM against NO and PGE2	LR Lei *et al.,* 2022
34	Flavoglaucin (103) Isotecra hydroauroglaucin (104)	Polyketides	Eurotium sp. SF-5989	against NO and PGE2 in LPS-activated RAW264.7 cells	J Xu *et al.,* 2019
35	Cytarabine	Other compounds	Sponge	DNA synthesis inhibition	MF Siddiqui *et al.,* 2018
36	Bryostatin	Other compounds	Bryozoa	PKC activation	GE Keck *et al.,* 2011
37	Dolastatin 10	Other compounds	Sea hare	Pro-apoptotic effects and inhibition of microtubules	P Schöffski *et al.,* 2004
38	Ecteinascidin 743	Other compounds	Tunicate	Alkylation of DNA	J Jia *et al.,* 2023
39	Aplidine	Other compounds	Tunicate	Inhibits cell progression cycle	X Jing *et al.,* 2020
40	Halichondrin B	Other compounds	Sponge	Interaction tubulin	R Bharti and SK Shukla et al.,2021
41	Discodermolide	Other compounds	Sponge	Stabilization tubulin	X Liang *et al.,* 2019

42	Spirulan	Other compounds	Algae	Inhibition heparanase	AA Shahapurkar *et al.*, 2022
43	Tolyporphin	Other compounds	Algae	Inhibition of acyl CoA: cholesterol-Oacyl transferase	AR Carroll *et al.*,2022
44	Stypodiol	Other compounds	Algae	Promotion of tubulin polymerization	JB Adetunji *et al.*,2023
45	Cytrabine	NA	Sponge	DNA Alkylation	A Pagidipally *et al.*, 2023
46	Bryostatin	NA	Bryozoa	PKC activation	Z Tian *et al.*, 2023
47	Dolastatin 10	NA	SeaHare	Pro- apoptotic effects and inhibition of microtubules	P Sekar *et al.*, 2022
48	Ecteinascidin 743	NA	Tunicate	Alkylation of DNA	J Jia *et al.*, 2023
49	Aplidine	NA	Tunicate	Inhibits cell cycle progression	X Jing and K Jin, 2020
50	Halichondrin B	NA	Sponge	Interaction with tubulin	IP Singh *et al.*, 2021
51	Discodermolide	NA	Sponge	Stabilization with tubulin	MK Gupta *et al.*, 2023

52	Spirulan	NA	Algae	Inhibition of heparanase	Shahap urkar *et al.,* 2022
53	Tolyporphin	NA	Algae	Inhibition of acyl CoA: cholestrol-O-acyl transferase	TP Kubrak *et al.,* 2022
54	Stypodiol	NA	Algae	Promotion of tubulin polymerization	B Adetunji *et al.,* 2023

Bioactive compounds from cyanobacteria

Cyanobacteria (blue-green algae) are photosynthetic prokaryotes used as food by humans. They belong to the kingdom Monera and division Cyanophyta. They are among the most primitive forms of life on earth. Their cellular structure is simple prokaryote and performs photosynthesis, resembling plants but lack plant cell walls resembling primitive bacteria.At the time, cyanobacteria are one of the most intriguing sources of new marine chemicals. Cyanobacteria have been utilised in medicine since 1500 BC, when Nostoc species were employed to treat gout, fistulas and cancer. Anti-fungal, anti-inflammatory, anti-cancer and anti-HIV agents are among them (NS Younis *et al.,* 2022).

Some of the high value metabolites from cyanobacteria are:

1)Cyanovirin-N (CV-N) is a unique, 101 amino acid long, 11 kDa protein. It was discovered as a constituent of a cultured cyanobacterium, Nostoc ellipsosporum, and both the sequence and the 3-D structure of CV-N are unprecedented. CV-N potently and irreversibly inactivates diverse primary strains of HIV-1, including Mtropic forms involved in sexual transmission of HIV. CV-N also blocks cell-to-cell transmission of HIV infection. CV-N is directly virucidal (Burja *et al.,* 2001).

2)Borophycin is a boron containing metabolite isolated from marine strains of cyanobacteria Nostoc linckia and Nostoc spongiaeforme var. tenue. It exhibits potent cytotoxicity against human epidermoid carcinoma and human colorectal adenocarcinoma cell lines and has been found to exhibit antimicrobial activity (Burja *et al.*, 2001)

3) Cryptophycin: It was first isolated from Nostoc sp. ATCC 53789 is a potent fungicide. It was also found to be very toxic and disregarded as natural product. It has also been isolated from Nostoc sp. GSV 224 and has

exhibited potent cytotoxicity against human tumor cell lines. It shows good activity against a broad spectrum drug-sensitive and drugresistant murine and hu man solid tumors (Burja *et al.,* 2001).

4) Lipopeptides Approximately 68% of the natural products derived from cyanobacteria contain nitrogen. Lipopeptides are interesting and biochemically active, having cytotoxic, anticancer, antibiotic, enzyme inhibitor, antiviral and antifungal activities (Burja *et al.,* 2001). Hapalosin ,a cyclic desipeptide isolated from the cyanobacteria, Hapalosiphon welwitschii, has a reversing activity against MDR (multi drug resistance) derived from Pglycoprotein (Kashihara *et al.,* 2000).

5)Protease Inhibitor: Five classes of protease inhibitors have been reported from the toxic genera of cyanobacteria: they are micropeptins, aerugenosins, microginins, anabaenopeptins and microverdins. Some cyanopeptolins are specific inhibitors of serine proteases, including elastase, which is of critical importance in a number of diseases like lung emphysema, which is mediated by excessive action of elastase (Raposo *et al.*, 2015).

Some of the toxins from cyanobacteria are:

1)Hepatotoxins: Cyanobacterial hepatotoxins, including microcystins (MCs) and nodularins (NODs), are widely produced, distributed and extremely hazardous to human beings and the environment.Microcystis aeruginosa and Nodularia spumigena synthesize toxins are destructive to liver cells. To date over 50 different variants of microcystins have been isolated from the species of Anabaena, Hapalasiphon, Microcystis, Nostoc and Oscillatoria. Biological activities of Lyngbya majuscula are very diverse and the compounds include potent protein kinase C activators and tumor promoters like lyngbyatoxins and aplysiatoxins (microlides) (Qianwen *et al.,* 2022)

2) Kalkitoxin: It is a neurotoxin.Painkillers like lidocaine are sodium channel blockers. Kalkitoxin could treat neurodegenerative diseases by selectively activating and blocking sodium channels, thus is a useful pharmaceutical compound and a valuable tool to understand the working of sodium channels and the effect of disease on them (Wu *et al.,* 2000).

3)Antillatoxin: This lipodesipeptide toxin is an extremely potent ichthyotoxin. Its activity is comparable to that of brevetoxin and involves the activation of voltage-gated sodium channels (Yokokawa *et al.,* 2000).

4) Barbamide: Barbamide was isolated from a Curac¸ao strain of L. majuscula and is known to be molluscicidal. Although it is a small molecule, barbamide has complex structural and biosynthetic features, including a thiazole ring and a biosynthetically intriguing trichloromethyl group (Andrea *et al.,* 2023).

5) Saxitoxin: Saxitoxins are neurotoxic alkaloids, which are known as paralytic shellfish poisons. Alexandrium catenella, A. minutum, A.ostenfeldi, A. tamarense, Gymnodinium catenatum and Pyrodinium bahamense secrete saxitoxins. Saxitoxin is 1000 times more toxic than the potent nerve gas sarin. This neurotoxin specifically and selectively binds to the sodium channel in neural cells. Thus, it physically occludes the opening of Na+ channels and prevents any sodium cation from going in or out of the cell. (Ahmed Moustafa *et al.,* 2009).

6)Anatoxins: Anatoxin-a produced by Anabaene flos-aquae is a low molecular weight, watersoluble bicyclic compound and enters the body by inhalation, injection and exposure to high concentration through the skin (Yokokawa et al., 2000). Natural anatoxin-a is a (+) stereoisomer and is more toxic. Homoanatoxin-a is structurally similar to anatoxina found in Oscillatoria formosa (Lilleheil *et al.,* 1997).

7)Brevitoxins: Brevitoxins are neurotoxins produced by Ptychodiscus brevis, from which the name is derived. These are lipophilic compounds with a molecular weight of approximately 900 Da. It binds to the ion channel of nerve and muscle tissue that selectively allows sodium to pass into the cell (Ophélie Pierre *et al.,* 2021).

Table 3. Showing the list of bioactive compounds from various sources

S.NO.	COMPOUNDS	CLASS	SOURCES	ACTIVITY	REFERENCE
1	Polysaccharides	NA	*Chlorella*	Moisturizing and thickener agent	Jain *et al.,* 2005
2	Methanolic extracts of exo polysaccharides	NA	*Arthrospira platensis*	Antioxidant	Raposo *et al.,* 2015
3	Chrysolaminarin	NA	*Odontella aurita*	Antioxidant	Xia *et al.,* 2014
4	Sulfated polysaccharides	NA	*Porphyridium and Rhodella reticulata*	Antioxidant	Raposo *et al.,* 2015

5	Beta- 1,3-Glucan	NA	*Chlorella Skeletonema Porphyridium Nostoc flegelliforme*	Free-radical collector Immune system booster Antiinflammatory	Spolaore *et al.,* 2006 Koller *et al.,* 2014 Bin *et al.,* 2013
6	Beta- carotenes	NA	*Dunaliella salina*	antioxidant	Bin *et al.,* 2013
7	Asthaxanthin	NA	*Haematococus pluvialis*	Antioxidant Sunscreen protection	Koller *et al.,*2014
8	Phycocyanobilin	NA	*Spirulina*	antioxidant	Hamed *et al.,* 2016
9	Phycoerythrobilin	NA	*Porphyridium*	Antioxidant Pigment for eye-liner and lipsticks	Hamed *et al.,* 2016
10	Sulfolipid	Fatty acid (sulfo)	*Lyngbya lagerheimii, Phormidium tenue*	Anti-HIV-1 activity	Skulberg *et al.,* 2000
11	Barbamide	Chlorinated	*Lyngbya majuscula* *19L*	Antumollusciicidal	Chang *et al.,* 2004
12	Antillatoxin B	Cyclic lipopeptide	*majuscula*	Neurotoxic Ichthyotoxic,activator of voltage-gated sodiumchannel	Yokokawa *et al.,* 2000
13	Didemnin	Lipopeptide	*Synechocystis trididemni*	Anti cancer Antiviralimmunosuppresive	Mitchell *et al.,* 2000
14	Cylindrocyclophane	Alkaloid, macrocy	*Cylindrosoermum licheniforme*	Anti-cancer cytotoxic	Burja *et al.,* 2001

		cle			
15	Cylindropermopsi n	Alkaloid	*Cylindrospermopsi s raciborskii*	cytotoxic	Li *et al.*, 2001
16	Patellamide A,B,C and D	Cyclic lipopepti de	*Prochloron didemni*	Cytotoxic, biological activity against multi-drug resistant UO- 31	Schmidt *et al.*, 2005 Ramaswamy *et al.*, 2006
17	Lyngbyabellins A and B	Lipopept ides	*L . majuscula*	Cytotoxic, anticancer, cytoskeleton disruption	Yokokawa *et al.*, 2000
18	Antillatoxin B	Lipopept ide	*L . majuscula*	Neurotoxicichthyotoxic,activator of voltage-gated sodium channel, with sodium channel-activating	Yokokawa *et al.*, 2000
19	Semiplenamides A-G	Lipopept ide	*L . semiplena*	All displayed weak to moderate toxicity in brine shrimp assay	Tan *et al.*, 2007
20	Cyanovirin	Peptide and proteins	*N . ellipsosporum*	Anti- HIV-1	Singh *et al.*, 2011
21	Monogalactopyra nosylglycerol Digalac topyranosyl glycerol	Sulfolipi ds	*P. tenue*	Anti- HIV, anticancer	Hayashi *et al.*,2006
22	Calothrixin	Indoles	*Calothrix sp.*	Antimalarial,anticancer against HeLa epithelial carcinoma	Vijayakumar and *et al.*,2015

23	Symplostatin 1 Symplostatin 2	dolastati n 10	*Symploca hydnoides, Symploca sp.*	Against Murine colon 38 and murine mammary 16/ C cell lines	Luesch *et al.*, 2002
24	Lyngbyatoxins A- C		*Lyngbya majuscula*	Cytotoxic, ichthytoxic, tumor promoter, protein kinase C activator, skin irritant	Burja *et al.*, 2001
25	Hectochlorin	Lipopept ide	*L . majuscula*	Against colon, melanoma, ovarian and renal and lung cancer cell lines, promote actin polymerization	Marquez *et al.*,2002
26	Hermitamides A and B		*L . majuscula*	Ichthyotoxic, brine shrimp, toxicity, cytotoxic	Burja *et al.*, 2001
27	Somocystinamid e A	Lipopept ide	*Lyngbya majuscula*	Cytotoxic against neuro 2a neuroblastoma cells, pluripotent inhibitor of angiogenesis and tumor cell proliferation, induces apoptosis in endothelial cells	Wrasidlo *et al.*, 2008
28	Oscillatoxin	Aromaic	*Oscillatoria nigroviridis*	Anticancer, toxic general	Burja *et al.*, 2001
29	Microviridin	Tricyclic depsipep tides	*Microcystic aeruginosa*	Antibiotic, anticancer	Han *et al*., 2006
30	Carmabin A - B	N-	*L . majuscula*	Anticancer, antiproliferative	Burja *et al.*, 2001

		Methylat ed peptide			
31	Scytonemin A	Caroteno ids	*Scytonema sp.*	Calcium antogonistic property	Helms *et al.*,1988
32	Bottromycin D	peptide	*Streptomyces sp.*	Anti - Bacteria	Helms *et al.*,1988
33	Perthamide C/D	cyclopep tide	*Theonella swinhoei*	Anti- inflammatory	Festa *et al.*, 2009
34	Perthamide G-K	cyclopep tide	*Theonella swinhoei*	Anti- inflammatory	Festa *et al.*, 2009
35	Perthamide E-F	cyclopep tide	*Theonella swinhoei*	Anti- inflammatory	Festa *et al.*, 2009
36	R-phycoerythrin, R-phycocyanin	peptide	*Gellidium pusillum*	Antioxidant, anticancer,neuropr otective,antiinflam matory	Mittal *et al.*, 2017
38	Phycocyanin	peptide	*Spirulina platensis*	Suppression of IL-6 and IL-8	Soria- Mercado *et al.*, 2009
39	Astaxanthin	KetoCaroten o	*Haematococcus pluvalis*	Reduction in FKN and MCP -1 level suppression of IL-6, IL-1beta and TNFalpha	Han *et al.*, 2006

		id			
40	Biseokeaniamide A	peptide	*Okeania sp*.	Suppression of IL-1 beta expression	Burja *et al*., 2001
41	Fucoxanthin	carotenoids	*Conticribara weisflogii*	suppression of IL-6, IL-1beta and TNFalpha	Singh *et al*., 2016
42	Mycosporine-2glycine	Amino Acid	*Alphanothece halophytica*	Suppression of COX-2 expression	Singh *et al*., 2011
43	Aeruginosin-865	Amino Acid, peptide	*Nostoc sp*.	Anti- Inflammatory	Yokokawa *et al*., 2002

Bioactive compounds from Fungi

Chytridiomycota, Oomycota, Ascomycota, Bacidomycota, Deuteromycota and Zygomycota are the phyla of marine fungus. Marine fungi, like marine bacteria, frequently exist as symbionts in algae or marine animals, particularly sponges. Collection of marine fungi typically necessitates the collection of the host or supporting material (e.g., algae, marine animals, sand or water), which presents difficulties in maintaining vitality until extraction. The majority of fungal species isolated from sponges are from the genera Aspergillus and penicillium. Every year, some 150-200 novel compounds are identified from marine fungi, and the number is growing. Polyketides, sesquiterpenes, alkaloids and aromatic compounds are examples of compound classes. Although no marine fungus-based drugs are currently under development, fungi metabolites have shown promising cytotoxic, neuroactive, antibacterial, antiviral and antifungal activity.Chaetomium globosum is a hydrophilic fungal species and a contaminant of water-damaged building materials in North America. Recently research article describes the production of a Chaetomium globosum enolase monoclonal antibody. Asteltoxins with Antiviral Activities were isolated from the Marine Sponge-Derived Fungus Aspergillus sp. SCSIO XWS02F40 exhibited inhibitory activity against H1N1 (N Suwannarach *et al.,* 2020).

Table 4. Showing the List of Bioactive Compounds from Fungi-

S.NO.	COMPOUND	SOURCE	ACTIVITY	REFERENCE
1	Isocoumarin derivatives	*Penicillium funiculosum*	Antibacterial activity	Zhuang Ding *et al.,* 2019
2	Polyketides	*Phomopsis sp. CFS42*	Antifungal	KL Ma *et al.,* 2020
3	Azaphilone alkaloids	*Chaetomium globosum*	Anticancer	F Huang *et al*., 2020
4	Phenolics and Flavanoids	*Alternaria alternata*	Antioxidant properties	S Chatterjee *et al.,* 2019
5	Amide derivatives	*Mycospharella nawae ZJLQ129*	Immunosuppre sant activity	LW Wang *et al*.,2017
6	Chromanones	*Phomopsis sp. CGMCC No. 5416*	Antiviral	LW Wang *et al*.,2017
7	Polyols	*Gliocladium sp. MR41*	Antitubercular	A Shah *et al.,* 2016
8	Ferulicacid,cinnamic acid, quercetin and rutin	*Penicillium roqueforti and*	Antibacterial	M Ikram *et al*., 2019

		Trichoderma reesei		
9	Dl- Mevalonic acid lactone, Methyl 6-O[1methylpropyl]a-dgalactopyranos ide	*Lasiodiplodia pseudotheobromae and PAK7 and Ltheobromae*	Antibacterial	Chaithra M *et al.,* 2020
10	Pentyl2H-pyran2one (6-PP)	*Trichoderma asperellum T1*	Antifungal and plant promoting properties	Chaithra M *et al.,* 2020
11	Phenylpropionic acid,5'-hydroxyasp erentin	*Cladosporium cladosporioides*	Antifungal	P Wonglom *et al*., 2020
12	Talaromyolide K	*Talaromyces purpureogenus*	Antiviral activity	RS Yehia *et al.,* 2020
13	Asteltoxins	*Aspergillus sp.*	Antiviral activity	Cao et al., 2020
14	1,4-diaza-2,5dioxo-3isobutylbicyclo[4.3.0]	*Diaporthe schini*	Antioxidant	YQ Tian et al., 2015
15	Hexahydropyrrozilin-3-one and (2-methylpropyl) ester	*Botyoshaeria dothidea*	Antioxidant activity	P Seetharaman *et al*., 2017
16	Camptothecin	*Fusarium solani S-019*	Anticancer	BV Da Rosa *et al*., 2020
17	Flavonechrysin(5,7-dihydroxy flavone)	*Alternaria Alternata*	Anticancer	SP Druzian et al., 2020

18	18-DeshydroxyCytochalasin	*Diaporthe phaseolorum*	Antiparasitic	X Ran *et al.,* 2017
19	Brefeldinand heptelidic acid	*Phyllosticta capitalensi*	Antiparasitic	P Seetharaman *et al*., 2017
20	Fusarubin,3Omethylfusarubin and javanicin	*Fusarium solani*	Antitubercular activity	A Shah *et al.,* 2016

Management Of Diabetes

Lifestyle, Genetics and Medical Conditions

Type 2 diabetes Mellitus is caused mostly by lifestyle and genetic factors. A variety of lifestyle variables are known to have a role in the development of type 2 diabetes mellitus. These are physical inactivity, sedentary lifestyle, cigarette smoking, and excessive alcohol intake. Obesity has been linked to around 55% of occurrences of type 2 diabetes mellitus. Toxins in the environment may be contributing to the recent rise in the prevalence of type 2 diabetes (N Tzenios *et al.,* 2023).

There is a strong inheritable genetic link in type 2 diabetes mellitus; having relatives (particularly first-degree relatives) with type 2 diabetes significantly increases the chance of getting type 2 diabetes mellitus. Monozygotic twins show nearly perfect concordance, and around 25% of people with the condition have a family history of diabetes. TCF7L2, PPARG, FTO, KCNJ11, NOTCH2, WFS1, CDKAL1, IGF2BP2, SLC30A8, JAZF1, and HHEX were recently revealed to be strongly related with the development of type 2 diabetes mellitus. TCF7L2 (transcription factor 7-like 2 controls proglucagon gene expression and consequently the generation of glucagonlike peptide-1, and KCNJ11 (potassium inwardly rectifying channel, subfamily J, member 11) encodes the islet ATPsensitive potassium channel Kir6.2. Furthermore, obesity (an independent risk factor for type 2 diabetes mellitus) is highly inherited (S Verma *et al.,* 2017). Monogenic types, such as Maturity-onset diabetes of the young (MODY), account for up to 5% of cases. Acromegaly, Cushing's disease, thyrotoxicosis, pheochromocytoma, chronic pancreatitis, cancer, and medications are some of the other reasons (H Zakaria *et al.,* 2023).

Pharmacological Agents: Role of synthetic drug in management of diabetes

Biguanides has various therapeutic applications of drugs containing biguanide group such as antimalarial, antidiabetic, antiviral, anticancer, antibacterial, antifungal, anti-tubercular, antifilarial, anti-HIV, as well as other biological activities. Metformin is a well-established first line drug for the treatment of type 2 diabetes mellitus. It suppresses hepatic glucose production, increases insulin sensitivity, increases glucose uptake by phosphorylating GLUT-enhancer factor, increases fatty acid oxidation, and decreases gastrointestinal glucose absorption. Metformin should be used with caution in elderly diabetics with renal impairment due to the risk of developing lactic acidosis. In comparison to sulfonylureas, it has a low incidence of hypoglycaemia (Collier CA *et al.,* 2006). It also appears to exert additional pleiotropic effects that are mediated by multiple epigenetic modifications (R Giordo *et al.,* 2023) . Metformin can also inhibit gluconeogenesis in the liver in an AMPKindependent manner by suppressing glucagon signalling (R.A. Miller *et al.,* 2013).

Sulfonylureas are potent glucose lowering drugs.They are traditionally added after metformin failure, are inexpensive, readily available everywhere and they are still the most frequently used second-line treatment for T2D in many parts of the world (Brian Tomlinson *et al.,* 2022). Although these are generally well tolerated, there is a risk of hypoglycemia because they stimulate endogenous insulin secretion When compared to younger patients, elderly patients with DM who are treated with sulfonylureas have a 36% increased risk of hypoglycaemia. Sulfonylureas differ in their selectivity for pancreatic beta-cells and in their risk for cardiovascular events and hypoglycemia with the most favorable profile seen with gliclazide followed by glimepiride and glipizide (Leyla Karkhaneh *et al.,* 2022).

Meglitinides act similarly by regulating adenosine triphosphate (ATP)-sensitive potassium channels (K-ATP channels) in pancreatic beta cells, thereby increasing insulin secretion, though binding site is different (Joseph Timmons and James Boyle *et al.,* 2022). Meglitinides have a rapid onset and short duration of action (J Philip and CJ Fernandez *et al.,* 2021). They are taken before meals to control postprandial blood glucose levels. Repaglinide and nateglinide are short-acting glucose-lowering drugs for therapy of patients with type 2 diabetes, thus lower risk of hypoglycemia. Meglitinides are pharmacologically distinct from sulfonylureas and may be used in patients who have an allergy to sulfonylurea medications. Repaglinide is particularly useful in patients with chronic kidney disease who cannot or prefer not to take other glucose-lowering medications (MO Mahgoub *et al.,* 2023). Repaglinide is principally metabolized by the liver, with less than 10 percent renally excreted. Thus, it can be used safely in patients with nondialysis chronic kidney disease (eg, estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m2) (WR Lin *et al.,* 2023).

Thiazolidinediones (rosiglitazone, pioglitazone) are oral insulin-sensitizing medications used in type 2 diabetes mellitus that reduce glucose with minimal risk of hypoglycemia .It is a selective ligand for the transcription factor peroxisome proliferator-activated gamma and the class, now consists primarily of pioglitazone following

the Food and Drug Administration (FDA) recommendation to restrict the use of rosiglitazone due to increased cardiovascular events reported with rosiglitazone (AB Olokoba *et al.,* 2012). However, thiazolidinediones can cause fluid retention thereby increasing the risk of heart failure which is a common complication of type 2 diabetes mellitus (CV Rizos *et al.,* 2016).Pioglitazone does not cause hypoglycemia and can be used in cases of renal impairment, making it well tolerated in older adults. Concerning about peripheral edoema, fluid retention, and fracture risk in women, its use in older adults with DM may be limited. Pioglitazone is contraindicated in patients with class III-IV heart failure and should be avoided in elderly patients with congestive heart failure (FS Yen *et al.,* 2023).

Currently, only three alpha-glucosidase inhibitors are utilized in clinical practice: acarbose, miglitol and voglibose, thus research efforts seeking novel inhibitors with improved efficacy are increasing (U Hossain *et al.,* 2020). These medications work best for postprandial hyperglycemia and should be avoided in patients with severe renal impairment. Because of the high rate of side effects such as diarrhoea and flatulence, their use is usually restricted (SR Joshi *et al.,* 2015). The newest of the drugs, voglibose, has been shown in a study to significantly improve glucose tolerance in terms of delayed disease progression and the number of patients who achieved normoglycemia. Reports have shown that alpha-glucosidase was 1.5-fold overexpressed in noninsulin-dependent diabetes patients contributing to the increase in postprandial glucose levels (Dyer *et al.,* 2002).

Incretins are gut-derived peptides secreted in response to meals, specifically the presence and absorption of nutrients in the intestinal lumen.1 The major incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). (Inzucchi and Darren K. McGuire *et al.,* 2008). GLP-1 analogues form the foundation of incretin-based therapies that aim to target this previously unknown feature of DM pathophysiology, resulting in sustained improvements in glycemic control and body weight control (Stonehouse AH *et al.,* 2011). In adults with type 2 diabetes, they can be used as monotherapy, as an adjunct to diet and exercise, or in combination with oral hypoglycemic agents. Exenatide, an incretin mimetic, and Liraglutide are two examples (Chiniwala N *et al.,* 2011). The use of GLP1 therapies poses no risk of hypoglycemia (unless combined with insulin secretagogues). Furthermore, new evidence suggests that incretin-based therapies may benefit inflammation, cardiovascular and hepatic health, sleep, and the central nervous system (Stonehouse AH *et al.,* 2011).

DPP(Dipeptidyl-Peptidase) IV inhibitors inhibit DPP-4, a ubiquitous enzyme that rapidly inactivates both GLP1 and GIP, increasing active levels of these hormones and, as a result, improving islet function and glycemic control in type 2 diabetes (Pratley RE and Salsali A *et al.,* 2007). DPP-4 inhibitors are a new class of anti-diabetic drugs that are as effective as current treatments. They are effective as monotherapy in patients with

inadequate diet and exercise control, as well as as add-on therapy in combination with metformin, thiazolidinediones, and insulin.

Insulin is a peptide hormone secreted by the β cells of the pancreatic islets of Langerhans, maintains normal blood glucose levels, facilitates cellular glucose uptake, regulates carbohydrate, lipid , protein metabolism and promotes cell division and growth through its mitogenic effects.Insulin can be used alone or in conjunction with other oral hypoglycemic agents. If some beta cell function remains, augmentation therapy with basal insulin is beneficial. If beta cell exhaustion occurs, basal-bolus insulin must be replaced (N Tzenios *et al.,* 2023). In cases of glucose toxicity, rescue therapy with replacement is required, which should mimic the normal release of insulin by pancreatic beta cells (SSA Mageed *et al.,* 2023). Insulin is available in four different injectable forms: rapid acting, short acting, intermediate acting, and long acting. When compared to short acting forms, long acting forms are less likely to cause hypoglycaemia (GA Puckrein *et al.,* 2023).

Insulin analogues were developed to try and achieve more physiological insulin replacement from injection in the subcutaneous site (MA Jarosinski *et al.,* 2021). Their pharmacokinetics and pharmacodynamics differ from human insulin when injected subcutaneously(AK Sharma *et al.,* 2019).The rapid-acting insulin analogues, lispro, aspart and glulisine, have a rapid onset of action and shorter duration of action.They appear to improve postprandial glucose, incidence of hypoglycaemia and patient satisfaction and, when used in combination with basal insulin analogues, improve glycosylated haemoglobin in comparison to conventional insulin therapy (B Sheldon *et al.,* 2009).

Future in Drug Therapy Inhaled Insulin

The inhaled form of rapidly acting insulin that became available in 2006 after being approved by both the European Medicines Evaluation Agency and the Food and Drug Administration for the treatment of type 1 and type 2 diabetes in adults. It is a rapid-acting insulin that has been approved for use in adults with type 1 and type 2 diabetes and has the advantage of being delivered directly into the lungs. However, studies have shown that inhaled insulin is as effective as, if not more so than, short acting insulin. Due to poor sales, the manufacturer removed it from the market in October 2007(Rosenstock J *et al.,* 2010).

Role Of Bioactive Compounds in Management of Diabetes

Several therapeutic strategies have been shown to be highly efficient in lowering acute and chronic inflammation, as well as alleviating diabetes and its consequences, via indirect or pleiotropic processes. Reducing inflammation (especially major inflammatory markers such as pro-inflammatory mediators TNF, IL-6, IL-1, and CRP) could be a critical public health intervention in lowering the burden of diabetes and associated

consequences such as cardiovascular disease in the general population. The possibility of controlling innate immunity-related inflammation as an essential experimental technique for the management/prevention of T2DM is supported by research into the therapeutic efficacy of anti-inflammatory drugs (Badawi *et al.*, 2010).Sulfonylureas, metformin, and insulinsensitizing glitazones are now the main therapeutic drugs used to treat T2DM and its consequences (G Goodarzi *et al.*, 2023). They all improve metabolic control and lead to the regulation of numerous circulating inflammation mediators via innate immunity-related signalling pathways. Sulfonylureas and metformin are the most often used medications to prevent T2DM. Sulfonylureas boost insulin production from pancreatic -cells, whilst metformin decreases glucose synthesis in the liver while increasing insulin sensitivity in peripheral tissues (Rendell and M *et al.*, 2004). Another anti-diabetic medicine, glitazones, interacts to peroxisome proliferator-activated receptors (PPARs), initiating a transcriptional activity that leads to enhanced insulin action by lowering inflammatory marker release. As a result, glitazones lowered CRP, PAI-1, TNF-, and other inflammatory markers. These medicines have a better anti-diabetic effect and a comparable antiinflammatory potential (Badawi *et al.*, 2010). Other therapeutic options for T2DM that operate as principals in the inflammatory system have been developed, including salicylates, an anti-inflammatory therapy that inhibits IB kinase (IKK), and reducing glucose levels through improved beta cell activity (Shoelson *et al.*, 2003). Various wellestablished NSAIDs and cyclooxygenase inhibitors (e.g., ibuprofen, naproxen) can increase glucose-mediated insulin release, glucose tolerance, and lower insulin resistance in diabetic individuals. NSAID treatment improved various biochemical markers in clinical investigations, including blood glucose level, glucose uptake, insulin clearance, CRP, lipid profile linked with obesity, and T2DM (Wilcox and G *et al.*, 2005). Saponin, myrcelin, flavonoids, pectin, and glucosides found in various portions of plants were found to have increased anti-diabetic properties. These phyto compounds have antidiabetic properties can differ depending on the mechanisms of their actions for decreasing glucose, which include glucose absorption, target insulin resistance, and pancreatic functions. Phyto bioactive components found in safflower and Japanese kelp extracts shown increased suppressglucosidase activity, controlling glucose absorption in the stomach (Zhang *et al.*,2013). Insulin, a soluble fibre, was found to regulate GLp-1 homeostasis in another investigation.Various phyto bioactive compound-rich plants, such as Dioscorea polysaccharides, blueberry anthocyanins, cinnamon, and fenugreek seeds, have been shown to further regulate insulin resistance(M.C *et al.*, 2014). Furthermore, various phyto extracts, including chilli peppers, bitter melon, ginseng, turmeric, and tea extracts, demonstrated a synergistic effect of these bioactivities. As a result, the synergistic efficacy of these phyto chemicals or the combinational intake of these meals will be a future research field in diabetes disease models. Despite the fact that these phyto chemicals demonstrated numerous positive effects in various in vitro studies, their extraction process limited their bioactivity. Diet and exercise are the cornerstones of treatment for both T1DM and T2DM (Wan *et al.*,2018). A diet high in fibre and monounsaturated fats and low in saturated fat, processed carbs, and high fructose corn syrup should be promoted. Aerobic exercise for 90 to 150 minutes per week is also

recommended. Weight loss is the primary goal of T2DM patients who are obese. Metformin is the first-line medication if sufficient glycemia cannot be attained. Following metformin, various additional medications such as oral sulfonylureas and DPP-4 inhibitors are used. There are glucagon-like peptide-1 (GLP-I) receptor agonists, sodium-glucose co-transporter-2 (SGLT2) inhibitors, pioglitazone, alpha-glucosidase inhibitors, and insulin available. Recent research has demonstrated that the SGLT2 inhibitor empagliflozin (EMPA) and the GLP-1 receptor agonist liraglutide prevent substantial CV events and mortality. As a result, in individuals with CV disease, these medications should be examined first. A basal-bolus insulin regimen is the basis of therapy for people with T1DM. In addition, insulin pump therapy is a viable option. Because hypoglycemia increases mortality, medications that do not generate hypoglycemia, such as DPP-4 inhibitors, SGLT-2 inhibitors, GLP-I receptor agonists, and pioglitazone with metformin, should be prioritised (EC Chao *et al.,* 2010). Other benefits of SGLT-2 inhibitors and GLP-Ireceptor agonists include decreased body weight, blood pressure (BP), and albuminuria .The aim HbA1C should be less than 7% to reduce microvascular problems in the majority of patients. In addition, the blood pressure aim should be less than 130/85 mmHg, with angiotensin-converting enzyme (ACE)/angiotensin receptor blocker (ARB) medication preferred. Guidelines recommend that fundal examinations and urine albumin excretion be performed at least twice a year. The target for the lipid panel should be LDL-C less than 100 mg/dl if no atherosclerotic cardiovascular disease (ASCVD) is present, or less than 70 mg/dl if ASCVD is present. Statins are the medicine of choice since they minimise CV events and mortality. Consider adding ezetimibe and PCSK9 inhibitors to the treatment regimen for individuals with ASCVD who are not at target. We have merely reviewed the concepts of treatment because the various complications and remedies have been covered in other StatPearls review articles (Shah SR *et al.,* 2019), (National guidelines for the prevention and control of diabetes in primary care, 2018).

Markers Of Diabetes

The phrase biological marker, or biomarker, is extensively used in medicine, biology, ecology, and environmental chemistry as a generic word for test findings on biological material that provide some indication of the status of the organism, environment, or ecosystem from which the sample was generated. This status may be related to exposure, susceptibility, effect, or risk. To assess dose effect levels, bioavailability, and, most importantly, safety of various nutraceuticals in specific cells and tissues, biomarkers that may serve to identify the potential of a phytochemical in the chemoprevention of certain diseases such as cancer, coronary heart disease, and advanced macular degeneration can be used. When examined in vitro and in vivo, a biomarker should be connected to the specific pathophysiology as well as the nutraceutical. The following examples show a method for determining the efficacy of a nutraceutical using various biomarkers. There are numerous definitions in the literature. The distinctions are due to the specific subject of the journal in which the definition is published, for example:A biomarker could be defined as a measurement made on body tissue, body fluid, or

excretion to provide a quantitative indication of exposure to a chemical and which may provide an estimate of the risks associated with that exposure.Pertaining to the topic of food chemistry a biomarker is defined as "any substance, structure, or activity that can be tested in the human body or its products and may impact or predict illness incidence or outcome." (Application of biomarkers in cancer epidemiology,1997), concerning cancer epidemiology "The biomarker would specifically and sensitively reflect a disease state and could be used for diagnosis as well as disease monitoring during and after therapy," says the study's lead author. , therapy-related Functionality also implies that a "biomarker is a molecule that signifies an alteration in physiology from normal and has clinical value,a definition that is limited only by its relationship to physiology and illness symptoms (Fung *et al.,* 2000).

Other broad definitions exist as well, for example, "biomarkers have been defined as indicators of actual or potential changes in systemic organ tissue, cellular and subcellular structural and functional integrity that can be used, either singly or in batteries, to monitor health and exposure to compounds in populations and individuals (Koletzko *et al.,* 1998). None of these definitions, including the consensus definition provided in response to the question above, are comprehensive enough to contain all of the properties of a biomarker. Two more definitions that are frequently stated in books are accuracy and specificity, for example, "one of the essential prerequisites of a (dietary exposure) biomarker is that it accurately represents intake of the dietary ingredients of interest (Wild CP *et al.,* 2001). The key properties of biomarkers responsiveness, specificity, ease of use, applicability, and relevanc apply especially in (diet and health).

Glucose-6-Phosphatase

Glucose homeostasis is tightly regulated and mainly controlled by regulating endogenous glucose production in the liver and glucose uptake by peripheral tissues in response to various hormones and nutritional signals. In the liver, de novo glucose production or gluconeogenesis is a focal point of regulation, and is repressed during feeding conditions and reactivated upon fasting to meet the fuel requirement of peripheral tissues (Nordlie *et al.,* 1999). The final step in the gluconeogenic pathway is catalyzed by the enzyme glucose6-phosphatase (G6Pase).

G6Pase is a multi-component membrane-bound system consists of a catalytic unit and transporter units for the substrate (glucose-6-phosphate) and products (glucose and inorganic phosphate) (van Schaftingen and Gerin, *et al.,* 2002). G6Pase's catalytic subunit is encoded by one of three genes, G6PC1, G6PC2, and G6PC3, but the antiporter that catalyses glucose-6-phosphate and inorganic phosphate transport is encoded by the SLC37A4 gene (Chou and Mansfield *et al.,* 2014). G6PC1 and SLC37A4 are both targets for hormone- and nutrition-dependent regulation of expression, which helps to control hepatic gluconeogenesis (Mihaylova *et al.,* 2011).

Insulin and glucagon, in particular, have a direct effect on G6PC1 gene expression. Insulin action is regulated by a multi-component insulin responsive unit made up of two regulatory regions in the proximal promoter labelled A and B. Region A binds HNF1, an auxiliary factor hypothesised to improve FoxO1 binding to two insulin response elements (IREs) inside Region B, termed IRE1 and IRE2 (Vander Kooi *et al.*, 2005). A third IRE, IRE3, is also present in Region B, although prior binding tests with a GST-FoxO1 fusion protein indicated that it does not bind FoxO1 (Vander Kooi *et al.*, 2005). Glucagon action, on the other hand, is mediated by CREB, which identifies the cAMP response element (CRE) inside Region B. (Oh *et al.*, 2013).

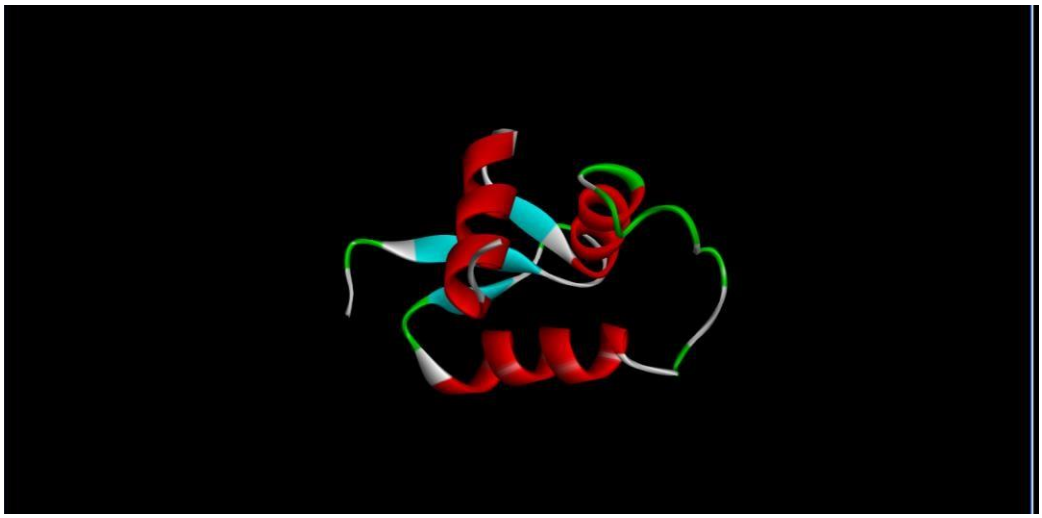


Figure 1. Showing the 3D Structure of Glucose-6-Phosphatase (G-6-P)

Glycogen synthase kinase-3 (GSK-3) is one of several downstream targets of the insulin activated signalling cascade, but it has unique features that set it apart from the others, making it an interesting drug development target in insulin resistance and Type 2 diabetes. GSK-3 was cloned for the first time in 1990 and has been proven to exist as two isoforms, and, which share 98 percent similarity in their catalytic domain. These isoforms are widely expressed in cells and tissues and have biochemical features that are comparable (but not identical). GSK-3 differs from other known intracellular protein kinases in that it is constitutively active in resting cells and is inhibited by extracellular signal activation. It was also shown that insulin inhibits GSK-3 activity; this appears to be a typical phenomenon in many cell types, including fibroblasts, adipocytes, and myoblasts. The inhibition of GSK-3 by insulin is achieved through the activation of phosphatidylinositol kinase-3 (PI3 kinase) and its downstream target, protein kinase B (PKB). PKB phosphorylation of GSK-3 on a serine site (Ser9 in GSK-3 and Ser21 in GSK-3) reduces enzyme activity. Notably, other protein kinases such as protein kinase C (PKC), cAMP dependent kinase (PKA), and the S6 ribosomal protein kinase p90RSK can inhibit GSK-3 by phosphorylating the same serine residue. This inhibition, however, may have physiological implications that

vary from those activated by insulin. Insulin-induced inhibition of GSK-3, for example, stimulates glycogen synthase activation, but epidermal growth factor or Wnt, which similarly inhibits the kinase, does not begin glycogen synthesis. This may be due to the longer duration of GSK-3 inhibition by insulin in comparison to other growth factors, as well as the fact that insulin activates other mechanisms, such as glucose absorption, which may function in tandem with GSK-3 inhibition to impact the specific physiological response. In conclusion, a number of extracellularly activated routes can inhibit GSK-3; however, the PI3 kinase/PKB pathway appears to be the major mechanism in insulin-induced GSK-3 inhibition.

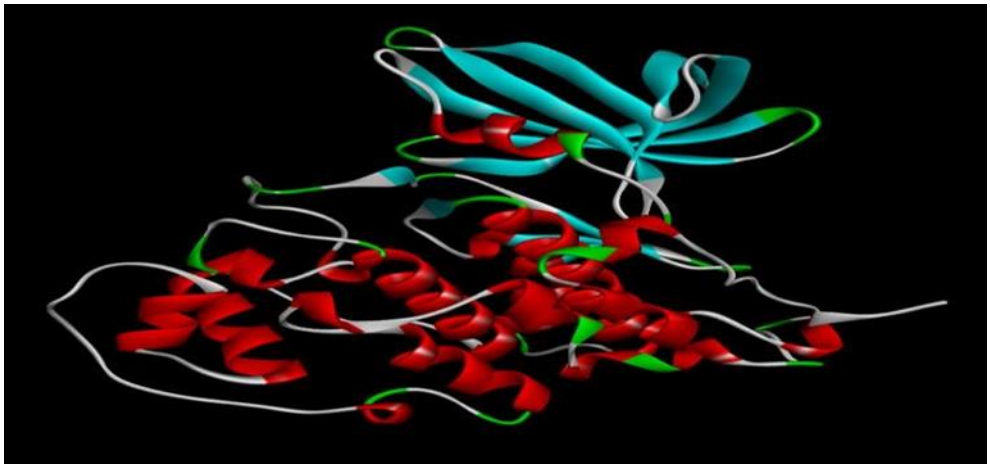


Figure 2. Showing 3D Structure of Glycogen Synthase Kinase 3-Beta

MATERIALS AND METHODS

Place of work

The present study entitled “Screening and evaluation of bioactive compounds from natural sources for antidiabetic potential: An in silico study” was carried out at IIRC-1, PTC-Lab, Computational biology laboratory Lab,Department of Bioengineering (Faculty of Engineering) Integral University, Lucknow.

Software used

Auto Dock 4.2, Cygwin, Discovery Studio 3.0 and 4.0 which runs on OS 64-bit Windows 7 or 64-bit Windows 11.

Cygwin

Cygwin is a Linux-like environment for Windows. It consists of two parts:

1.A DLL (cygwin1.dll), which acts as a Linux API emulation layer providing substantial Linux API functionality.

2.A collection of tools, which provide Linux look and feel.

As AutoDock4.2 is programmed to run on the Linux operating system, so for those systems, which run on Windows, Cygwin is a must. It can be freely downloaded from the Internet.

Auto dock tools 4.2

AutoDock4.2 is an automated procedure for predicting the interaction of ligands with bio macromolecular targets. The motivation for this work arises from problems in the design of bioactive compounds, and in particular the field of computer-aided drug design. Progress in bimolecular x-ray crystallography continues to provide important protein and nucleic acid structures. These structures could be targets for bioactive agents in the control of animal and plant diseases or simply key to the understanding of fundamental aspects of biology. The precise interaction of such agents or candidate molecules with their targets is important in the development process.

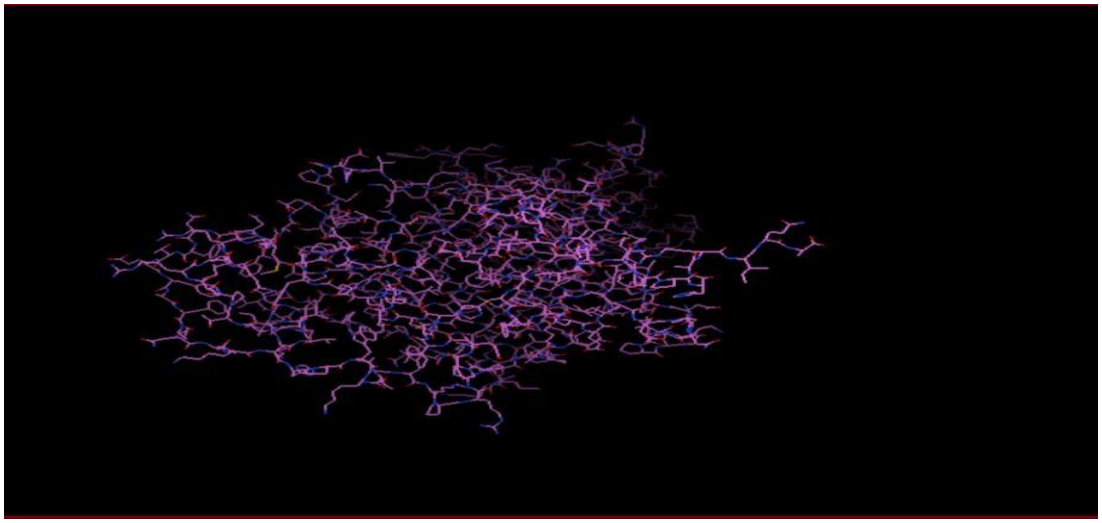


Figure 3. Showing Auto dock 4.2

Discovery Studio Visualizer

Discovery Studio is a comprehensive software suite for analyzing and modeling molecular structures, sequences, and other data of relevance to life science researchers. The Discovery Studio Visualizer is a free viewer that can be used to open data generated by other software in the Discovery Studio product line. It is designed to offer an interactive environment for viewing and editing molecular structures, sequences, X-ray reflection data, scripts, and other data.The application runs on Windows and Linux and is a fully integrated desktop environment.

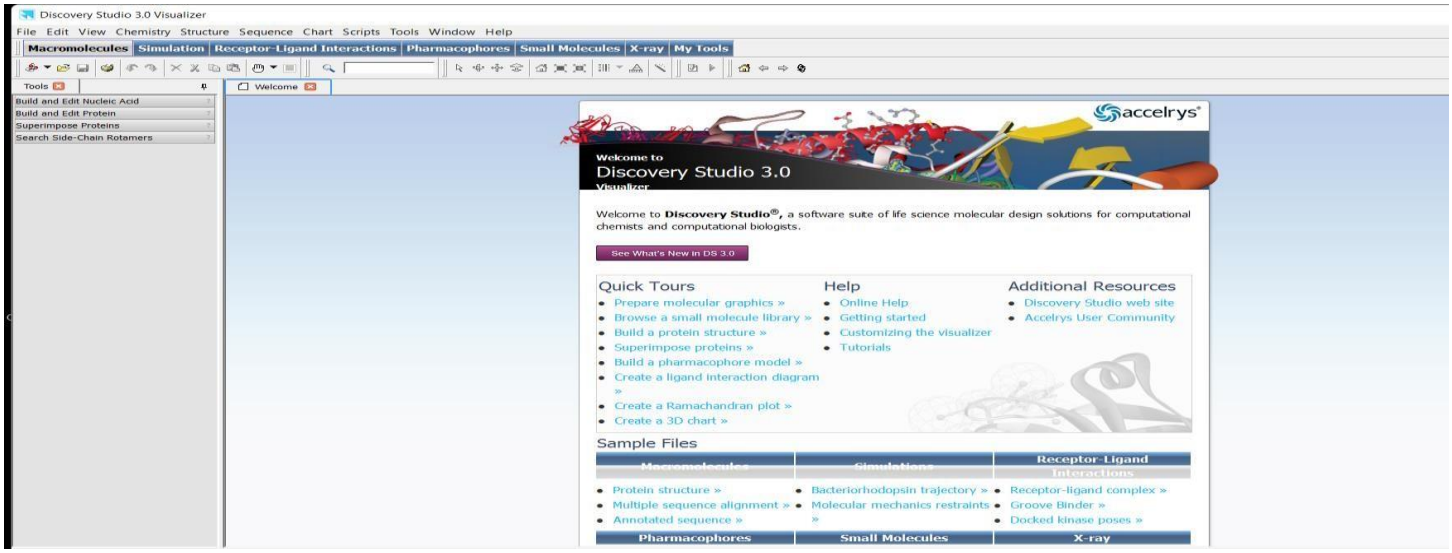


Figure 4. Showing Discovery studio

Molsoft

Molsoft offers software tools and services in lead discovery, modeling, cheminformatics, bioinformatics, and corporate data management; and forms partnerships with biotechnology and pharmaceutical companies. MolSoft is building unique technologies for structure prediction that improves our understanding of the spatial organization of biological molecules and their interactions with each other, their biological substrates and drug-like molecules at the atomic level. Application of these rules and algorithms to specific biomedical problems allows us to address the following problems:

- Molecule visualizing and data sharing
- Building and validating structural models of protein targets
- Identifying biological ligand binding sites or new sites for allosteric regulation of a protein of interest.
- Evaluating and ranking drug targets, including protein-protein interaction interfaces, designing strategies for rational drug design
- Screening virtual libraries of millions of compounds using the revolutionary Molsoft flexible docking and scoring procedure.
- Identifying interaction hot-spots, i.e., the candidate amino-acid positions involved in protein-protein interactions
- Predicting loop conformations in proteins
- Designing proteins with desired properties
- Docking flexible peptides to proteins
- Designing peptides blocking protein-protein interactions
- 2D to 3D conversion, analysis and clustering of large compound libraries,
- Predicting compound properties, building QSAR models, 3D pharmacophore construction and search
- Enterprise-wide cheminformatic databases.

PDB (Protein Data Bank)

The PDB archive contains information about experimentally-determined structures of proteins, nucleic acids, and complex assemblies. The RCSB PDB also provides a variety of tools and resources. Users can perform simple and advanced searches based on annotations relating to sequence, structure, and function. These molecules are visualized, downloaded, and analyzed by users who range from students to specialized scientists.

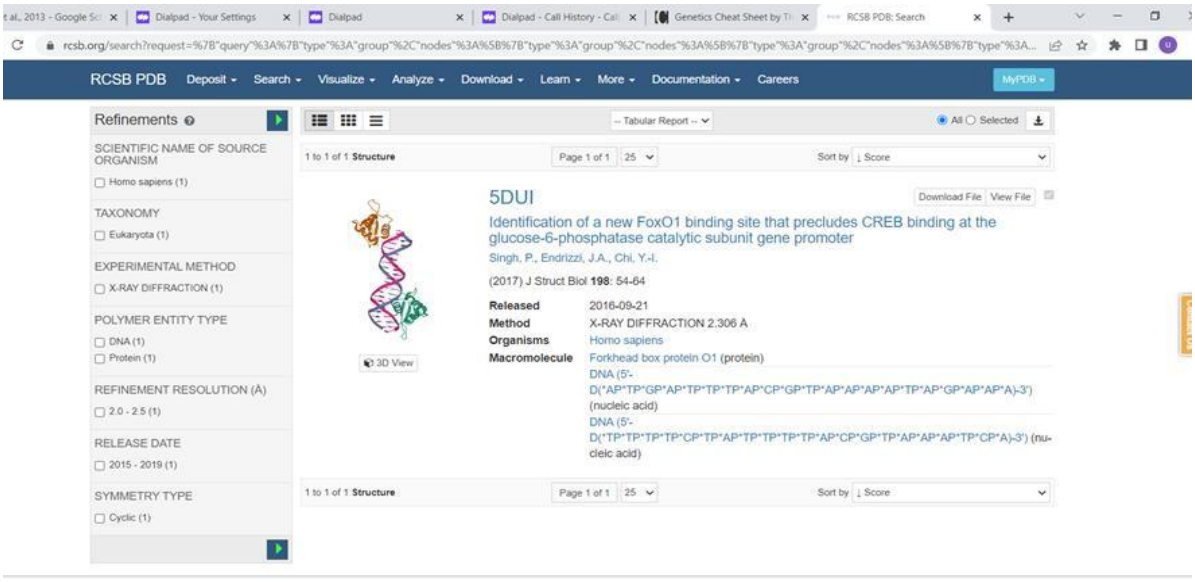


Figure 5. Showing PDB (Protein Data Bank)

PubChem

PubChem is an open chemistry database at the National Institutes of Health (NIH). “Open” means that you can put your scientific data in PubChem and that others may use it. Since the launch in 2004, PubChem has become a key chemical information resource for scientists, students, and the general public. Each month our website and programmatic services provide data to several million users worldwide.

PubChem mostly contains small molecules, but also larger molecules such as nucleotides, carbohydrates, lipids, peptides, and chemically-modified macromolecules. We collect information on chemical structures, identifiers, chemical and physical properties, biological activities, patents, health, safety, toxicity data, and many others.

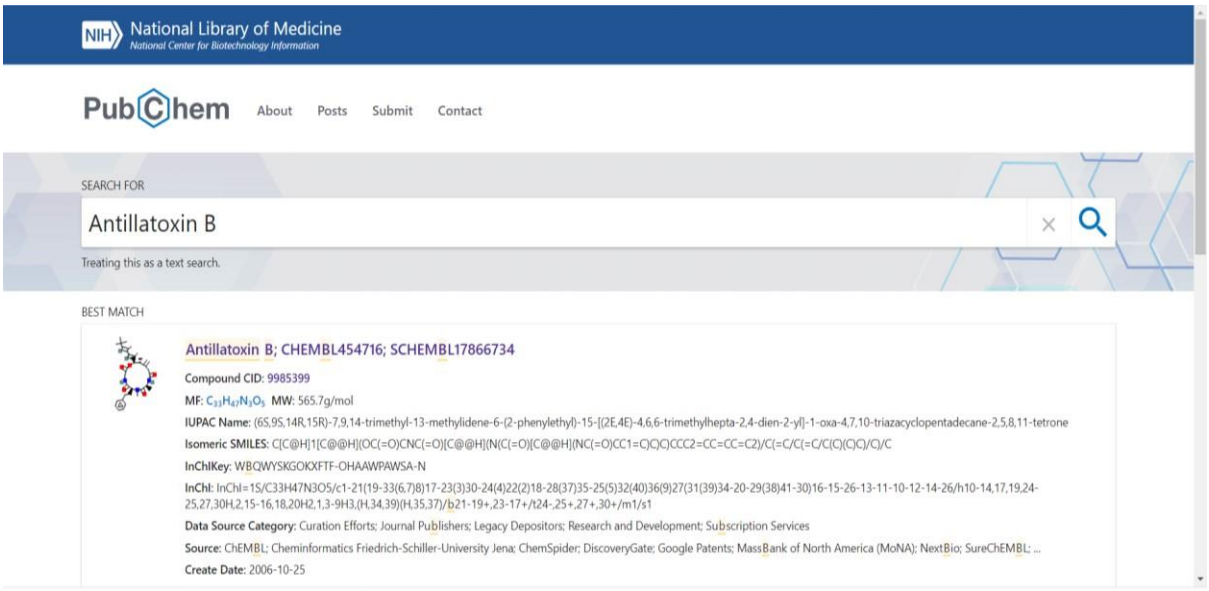


Figure 6. Showing PubChem

Docking Methodology

Drug Discovery

Drugs were discovered through identifying the active ingredient from traditional remedies or by serendipitous discovery. Imperial is keen to promote the discovery and development of pump prime the early stages of drug/therapeutic discovery within the Imperial Academic Health Science Centre (Imperial College London and Imperial College Healthcare NHS Trust environments).

Target-based drug discovery

Contemporary drug discovery and development (DDD) is dominated by a molecular targetbased paradigm. The primary explanation for low rates of new drugs is attrition or the failure of candidates identified by molecular target-based methods to advance successfully through the DDD process. Most drugs are inhibitors that block the action of a particular target protein. But the only way to be completely certain that a protein is instrumental in a given disease is to test the idea in humans. The most valuable application of high content screening to target validation is at the early stages of the process when genetic methods (including RNA interference-RNAi) are being applied to many potential targets (Moir *et al.*, 2005).

In silico studies

Auto Dock, Cygwin, Discovery Studio 4.0 which runs on OS - 32-bit Windows 7 SP3 or 64-bit Windows 7 or 64-bit Windows 10.

Preparation of target protein structure and ligands

Protein Data Bank (PDB) is a repository of 3-D structural data of biomolecules. The crystal structure of **Glycogen Synthase Kinase 3-Beta and Glucose-6-Phosphatase** was retrieved from it. All the water molecules and crystallographic substructures from the target protein were eliminated and the necessary hydrogen atoms were added along with Gasteiger- Marsili charges. The minimization process was undergone and protein protocol was automatically generated and the final structure was visualized in Discovery Studio Visualizer 4.0. A total of 20 bioactive compounds from cyanobacterial strains and 2 synthetic drugs were selected by the literature survey for docking studies and the bioactive compound structures were downloaded from Pubchem.

Protein-ligand docking

Docking of the target protein **G6P and GSK-3β** and the 20 ligands was performed for finding their binding affinities. Both the receptor and the ligand were optimized for proper geometry and the compounds were ranked. The best four compounds were selected based on the docking score and number of residues.

The 3-dimensional (D) structure of **G6P** (Glucose-6-phosphatase) and **GSK-3β** (**Glycogen Synthase Kinase -3β**) was withdrawn from Protein Data Bank (PDB ID: 2XKW and 3WQH respectively) use for docking study.

The Protein Data Bank (PDB) coordinates for the structure of Pioglitazone (CID: 4829), Metformin (CID: 4091) and Rosiglitazone (CID: 77999), Pyrazolopyrimidine (CID: 21083976), Benzimidazole (CID: 5798), Pyridinones

(CID: 135653775) were retrieved from 'Pub Chem' database. Thereafter, the ligands (Rosiglitazone, Metformin and Pioglitazone, Benzimidazole, Pyrazolopyrimidine,

Pyridinones were docked to the (**GSK- 3β and G-6-P)** using 'Autodock4.2'. For the energy minimization of the ligands molecule, the force field MMFF94 was used. Gasteiger partial charges were added to the ligands atoms. Non-polar hydrogen atoms were included, and rotatable bonds were defined. Docking calculations were proceeding on the protein model. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock 4.2. Affinity (grid) maps of 126×126×126 Å grid points and 0.375 Å spacing were generated using the Autogrid program aimed to target grid co-ordinates in proximity with the alpha-amylase and cyanobacterial bioactive compounds. To target the peripheral anionic site, several docking experiments were performed by placing the center of the grid at different well-recognized amino acid residues known to constitute the peripheral anionic site. The grid dimensions for targeting the active site used in this study are 126x126x126 Å. AutoDock parameter set and distance-dependent dielectric functions were used in the calculation of the Vander Waals and the electrostatic terms, respectively. The docking process was performed using the 'Lamarckian genetic algorithm' and the 'Solis & Wets local search method'. Initial position, orientation, and torsions of the ligands molecules were set randomly. Each docking experiment was derived from 20 different runs that were set to terminate after a maximum of 2,500,000 energy evaluations. The population size was set to 150. During the search, a quaternion and torsion steps and translational steps of 0.2 Å were applied. PDB coordinate files for the complexes showing ligands Antillatoxin B, Bastadin, Lyngbyatoxin A, Curacin D, Naringenin,

Catechin, and Carazostatin were retrieved from 'Pub Chem' database. Thereafter, the ligands (Antillatoxin B, Bastadin, Lyngbyatoxin A, Curacin D, Naringenin, Catechin, and Carazostatin) within the same active site were generated. The final figures were generated using Discovery Studio 4.0 (Accelrys).

Steps involved

1. The detailed study of the scientific literature available on Pub Med regarding **G6P** and the **GSK-3β**
2. To find pertinent x, y, z coordinate values to ensure targeted docking.
3. To dock the target protein and the inhibitor through the docking software AutoDock 4.2.
4. To elaborate molecular interactions of the docked complexes.

Tools used

- Molsoft
- AutoDock
- Discovery studio 4.0
- Cygwin
- ADMET

Databases used

- PDB (Protein Data Bank)
- UniprotKB
- PubChem

Table 5. Showing the Druglikeness of the bioactive compounds

S.NO.	CID NO.	NAME OF COMPOUND	SOURCES	ACTIVITY	Mol. Wt. (500 KD)	HBD	HBA	LOGP
1	11465376	Barbamide	*Lyngbya Mojuscula 19L*		460.05	0	4	4.60
2	10051827	Antillatoxin B	*Mojuscula*	Neurotoxic	503.34	2	5	4.00
3	9985399	Antillatoxin B	*L .Majuscula*	Neurotoxic	565.35	2	5	4.83
4	91706	Lyngbyatoxin A	*Lyngbya majuscula*	Cytotoxic, ichthytoxic, tumor promoter, protein kinaseC activator, skin irritant	437.30	3	2	5.40
5	131589	Lyngbyatoxin B	*Lyngbya majuscula*	Cytotoxic, ichthytoxic, tumor promoter, protein kinaseC activator,	453.30	4	3	4.42

				skin irritant				
6	6441239	Lyngbyatoxin C	*Lyngbya majuscula*	Cytotoxic, ichthytoxic, tumor promoter, protein kinaseC activator, skin irritant	453.30	4	3	4.31
7	636718	Hectochlorin	*L .Majuscula*	Against colon, melanoma, ovarian and renal and lung cancer cell lines, promote actin polymerization	664.11	1	13	4.81
8	10473646	Hermitamide A	*L .Majuscula*	Ichthyotoxic, brine shrimp,toxicity, cytotoxic	359.28	1	2	5.62
9	5280443	Apigenin	Parsley Oregano Celery	Attenuates the production of pro-inflammatory cytokines	275.05	3	5	3.22
10	5281224	Astaxanthin	Haematococcus pluvalis	Reduction in FKN and MCP -1level suppression of IL-6, IL-1beta and TNF-alpha	596.39	2	4	9.95
11	6438150	Asteltoxin	*Aspergillus stellatus*	mycotoxin	418.5	2	7	2.1
12	23427657	Mycosporine-2glycine	Alphanothece halophytica	Suppression of COX-2 expression	302.11	5	8	-3.31
13	440735	Eriodictyol	Lemon Mountain Balm		288.06	4	6	2.01

14	932	Naringenin	Grapefruit Oranges Tomatoes	Increases glucose tolerance insulin sensitivity	272.07	3	5	2.38
15	72281	Hesperetin	Lemon Orange Peppermint	Down-regulation pro-	302.08	3	6	2.51
16	6413514	Bastadin	*Ianthella quadrangulata, Aiolochroia crassa*	Exhibit calcium channel modulatory activity	1019.1	6	10	9.5
17	130857	Carazostatin	*Streptomyces chromofuscus*	Reduce the serum levels of pro-inflammatory cytokines	295.4	2	1	6.9
18	9064	Catechin	Green Tea Chocolate Beans	Suppress the activation ofNF-κB system through the inhibiton of pro-inflammatory cyto kines productions	290.08	5	6	0.53
19	10546404	Curacin D	*Lyngbya majuscula*	Reduce the elevation of inflammatory cytokines	359.6	0	3	5.5
20	8871	Pyridinones	Marine actinomycete	Antimicrobial	95.1	1	1	1.06
21	71768073	5’-Hydroxyasperentin	Cladosporium cladosporioides	Antifungal	308.13	3	6	1.74

22	15658290 3	Talaromyolide K	Talaromyces purpureogenus	Antiviral activity	444.21	3	7	3.53
23	6438150	Asteltoxin	Aspergillus sp.	Antiviral activity	418.20	2	7	2.64
24	6054	Benzeneethanol	Diaporthe schini	Antioxidant	122.07	1	1	1.29
25	189582	Hexahydropyrrol	Botyoshaeria dothidea	Antioxidant	125.08	0	2	0.03
26	213039	(2-methylpropyl) ester	Botyoshaeria dothidea	Antioxidant	547.24	4	8	2.72
27	24360	Camtothecin	Fusarium solani S-019	Anticancer	348.11	1	5	1.72
28	10410225	Noscomin	cyanobacterium Nostoc commune	Antibacterial	426.6	3	4	6.1
29	10749358	Nostocine A	cyanobacterium Nostoc commune	Antiparasitic	151.13	1	3	0.91
30	77999	Rosiglitazone	Penicillium chrysogenum	Antiparasitic	357.4	1	6	2.41

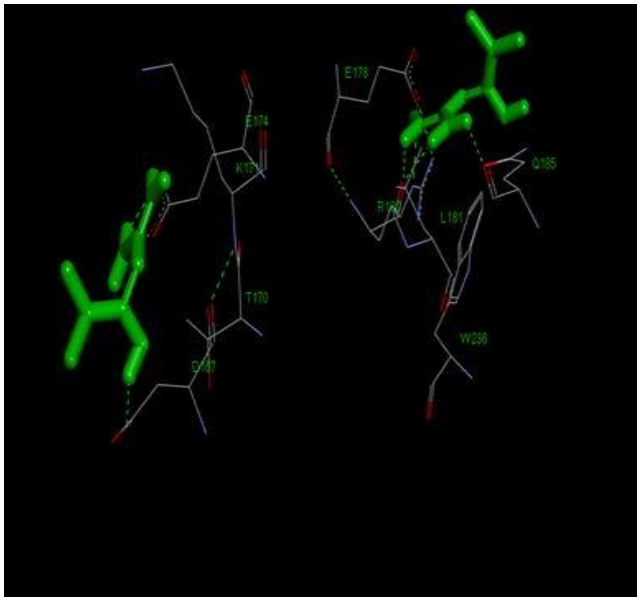
RESULTS AND DISCUSSION

Table 6. Shows Molecular Docking scores between bioactive compounds of cyanobacteria and diabetes marker Glycogen Synthase Kinase -3β (GSK-3β)

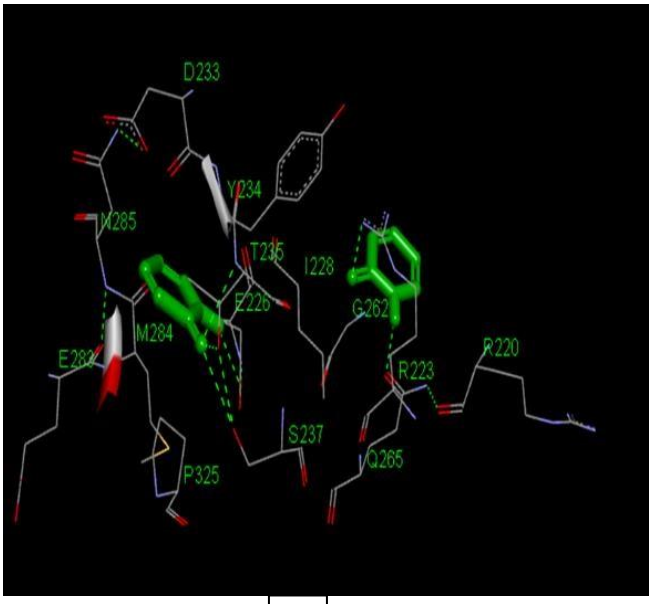
S.No.	Compound Name	Source	Activity	Docking Score (Binding Energy) Kcal/Mol	Inhibition Constant, Ki(μM)
1	**Pyrazolopyrimidine(Control)**	**Synthetic drug**	Antidiabetic	-3.46	2900
2	Antillatoxin B	*Lyngbya majuscula*	Antidiabetic	-7.16	5640
3	Bastadin	*Marine sponge*	anti-angiogenic	-6.98	7670
4	Benzimidazole	*Synthetic drug*	A ntidiabetic	-3.99	1190
5	Curacin D	*Lyngbya majuscula*	Antiproliferat i ve	-4.72	3444
6	Naringenin	*Plant*	Anticancer	-5.81	5508
7	Catechin	*Plant*	Antiinflamm atory	-5.35	1190
8	Pyridinones	*Synthetic drug*	Antidiabetic	-3.66	2080
9	Carazostatin	*Nostoc sp.*	Antibiotic and cytotoxic	-4.60	3640
10	Lyngbyatoxin A	*Lyngbya sp.*	Anticancer	-4.53	4769

Table 7. Shows Molecular Docking scores between bioactive compounds of cyanobacteria and diabetes marker Glucose-6-Phosphatase (G-6-P)

S.No.	Compound Name	Source	Activity	Dockingscore (binding energy) Kcal/mol	Inhibitio n Constant,Ki (µM)
1	**Metformin (CONTROL)**	**Synthetic drug**	Antidiabetic	-4.07	1040
2	Antillatoxin B	*Majuscula*	Antidiabetic	-6.69	1060
3	Lyngbyatoxin A	*Lyngbya sp.*	Antiinflammatory	-5.99	1044
4	Noscomin	*Nostoc commune*	Anti-diabetic	-5.15	1670
5	Rosiglitazone	*Synthetic drug*	Antidiabetic	-5.42	1071
6	Apigenin	*Plants*	Antiinflammatory	-5.27	1376
7	Asteltoxin	*Fungi*	Anti-diabetic	-4.85	2786
8	Barbamide	*Lyngbya majuscula*	Antioxidant	-1.49	8123
9	Mycosporine-2glycine	*Alphanothece halophytica*	Antiinflammatory	-4.58	4399
10	Nostocine A	*Cyanobacteria*	Anti-diabetic	-1.78	4998



a



b

Figure 7. Shows the a) Complex of Metformin and Glucose6-Phosphatase (G-6-P) And b) Complex of Pyridinones and Glucose-6Phosphatase (G-6-P)

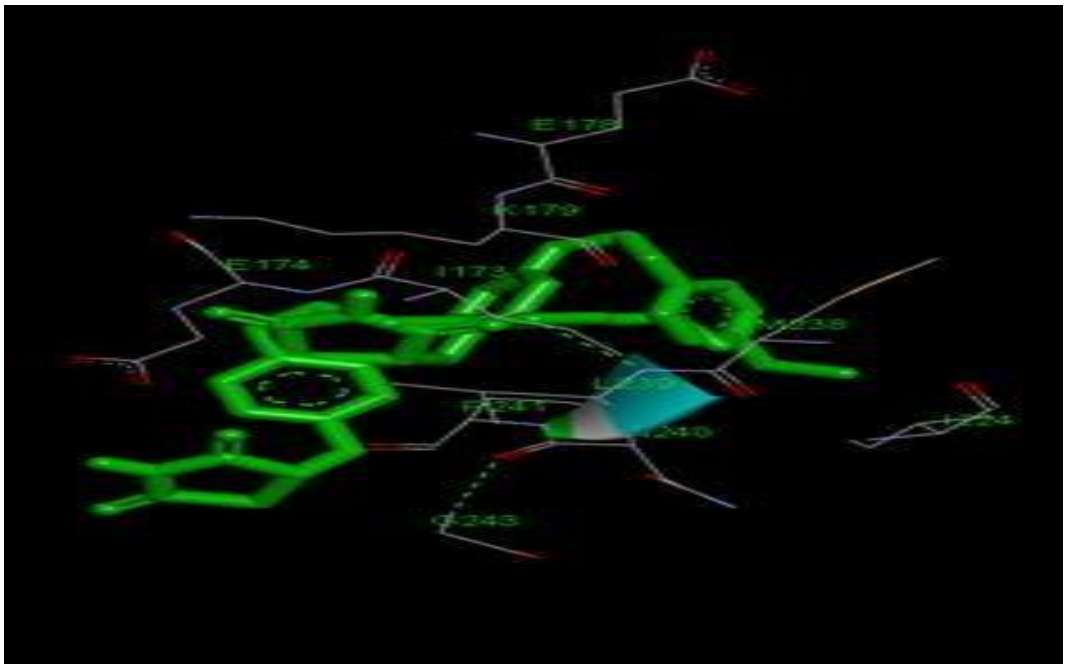
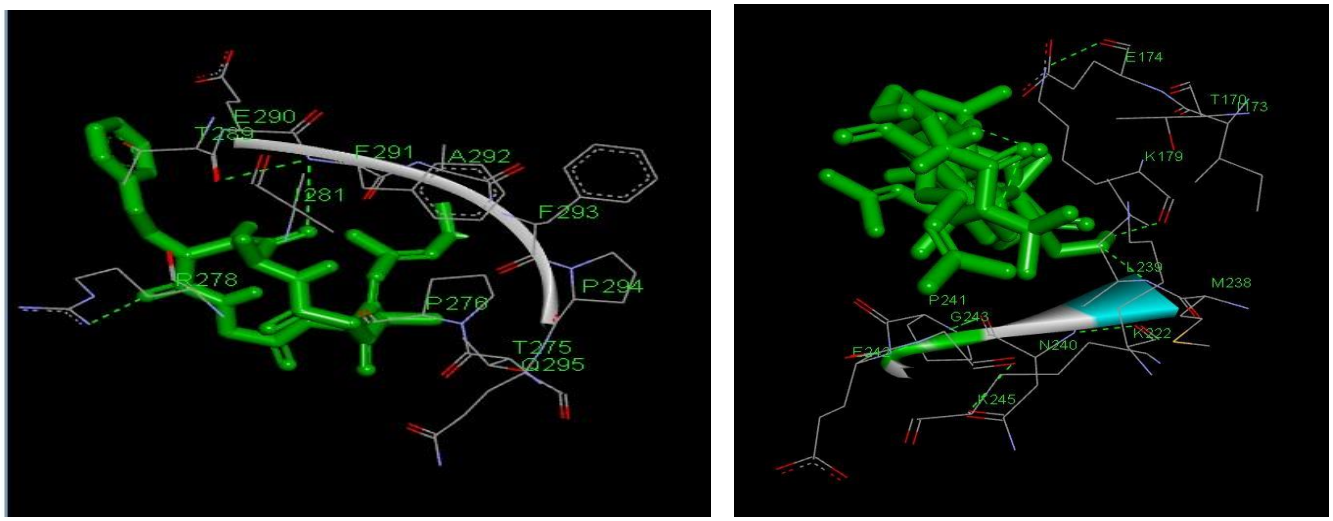
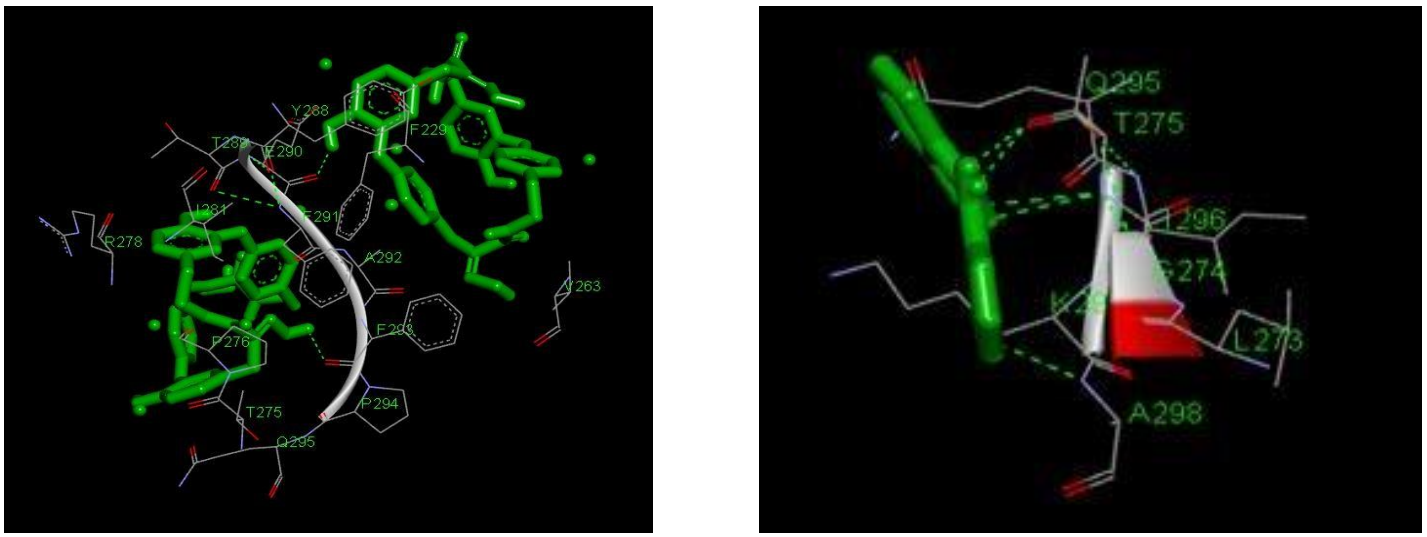


Figure 8. Shows the Complex of Rosiglitazone Glucose-6-Phosphatase (G-6-P)



a b

Figure 9. Shows the Complex of (a)Antillatoxin- B with Glycogen Synthase Kinase -3β and (b)Complex of Lyngbyatoxin A with Glucose-6-Phosphatase (G-6-P)



b a

Figure 10. Shows the (a)Complex of Bastadin and Glycogen Synthase Kinase -3β and (b)Complex of Pyrazolopyrimidine Glucose-6-Phosphatase (G-6-P)

Current advances in the understanding of the biology of Type 2 Diabetes Mellitus have resulted in a rising number of remedies that are approved or in clinical development for this disorder (Yarchoan and Arnold, 2014). In the present study, with the help of molecular docking approach we have been able to find out the interaction of selected anti-inflammatory markers which is associated with diabetes G-6-P (Glucose-6-Phosphatase) and GSK-3β (Glycogen Synthase Kinase-3β) with Cyanobacterial and other natural sources. Bioactive Compounds discover a promising link for the management of Type2 Diabetes Mellitus. The findings suggest that both G-6-P and GSK-3β, key enzymes involved in glucose metabolism, exhibit distinct interaction patterns with various pharmacological compounds. The interactions observed with Rosiglitazone, Pioglitazone, Lyngbyatoxin A, and Antillatoxin B indicate potential therapeutic targets for regulating glucose homeostasis.

Molecular interaction studies play a crucial role in unraveling the intricate mechanisms of biological processes. By examining how molecules interact with each other, scientists can gain valuable insights into the fundamental principles that govern life. In this present study the G-6-P (Glucose-6-Phosphatase) was found to interact with Rosiglitazone, Pioglitazone, Lyngbyatoxin A, Antillatoxin B. The other study is where the GSK-3β (Glycogen Synthase Kinase-3β) was found to interact with Metformin, Pyrazolopyrimidine, Antillatoxin B, Bastadin. These findings suggest that both G-6-P and GSK-3β have multiple interactions with various drugs and compounds. This highlights the potential for these proteins to play crucial roles in different biological processes and pathways. Further research is needed to fully understand the significance of these interactions and their implications for drug development and treatment strategies.

The binding energy determines the strength of interaction between a ligand and an enzyme. The lowest binding energy is the outcome of the best binding conformer at its receptor site or active site of an enzyme. This low binding energy allows for a strong and stable interaction between the ligand and the enzyme, promoting efficient enzymatic activity. Additionally, a low binding energy ensures that the ligand remains bound to the enzyme for an appropriate amount of time, allowing for proper catalysis and regulation of biological processes (Xu *et al*., 2008).

The docked ligands displayed acceptable binding energy values for G-6-P (Glucose-6-Phosphatase) and GSK-3β (Glycogen Synthase Kinase-3β). When compared to the standard control Pyrazolopyrimidibe, which shows -3.46 kcal/mol binding energy with an inhibition constant of 2900µM when taken for the in-silico analysis, the binding energy of antillatoxib B with the diabetes marker Glycogen Synthase Kinase-3β (GSK-3β) was found to be -7.16 kcal/mol with an inhibition constant of 5640µM. This indicates that antillatoxib B has a stronger binding affinity and inhibitory effect on GSK-3β. This shows that since GSK-3 β is a crucial enzyme for insulin signaling and glucose metabolism, antillatoxin B may be useful as a treatment for diabetes. Likewise, bastadin

had a binding energy of -6.98 kcal/mol and an inhibition constant of 7670 µM. This suggests that bastadin also has a strong binding affinity and inhibitory effect on GSK-3β, making it a potential candidate for diabetes treatment. In addition to their strong binding affinities and inhibitory effects on GSK-3β, antillatoxib B and bastadin hold promise for improving insulin signaling and glucose metabolism in diabetic patients. By targeting GSK-3β, these compounds have the potential to enhance insulin sensitivity and promote glucose uptake by cells. This could ultimately help regulate blood sugar levels and alleviate the symptoms of diabetes. However, further research is needed to determine the specific mechanisms by which antillatoxib B and bastadin exert their effects and to evaluate their safety and efficacy in clinical settings.

When compared to lyngbyatoxin, which had a higher binding energy of -5.99 kcal/mol and an inhibition constant of 1044 µM against the diabetes marker glucose-6-pjhodsphate, rosiglitazone demonstrated a binding energy of -5.42 kcal/mol and an inhibition constant of 1071µM. In contrast to the standard control used in this study, antillatoxin demonstrated a binding energy of -6.69 kcal/mol with an inhibition energy of 1060 µM. This is more than the metformin control, which demonstrated a binding energy of -4.07 kcal/mol with an inhibition constant of 1040 µM. Overall, the results show that both rosiglitazone and antillatoxin have higher binding energies and inhibition constants compared to the standard control metformin. This suggests that both rosiglitazone and antillatoxin may have greater potential for inhibiting the diabetes marker glucose-6-phosphate and may be more effective in treating diabetes. Further studies would be needed to evaluate the efficacy and safety of these compounds in a clinical setting.

Using the molecular docking approach, the current study has determined how specific anti-inflammatory markers linked to diabetes, such as GSK-3β (Glycogen Synthase Kinase) and G-6-P (Glucose-6-Phosphatase), interact with cyanobacteria and other natural sources. These results suggest that Cyanobacterial and other natural bioactive compounds such as Antillatoxin B, Bastadin, Lyngbyatoxin A, Curacin D, could serve as inhibitors for Type 2 Diabetes Mellitus. Furthermore, their natural origin makes them attractive candidates for the development of novel therapeutics, as they may have fewer side effects compared to synthetic drugs. Further research is needed to fully understand the mechanisms of action and assess the safety and efficacy of these compounds for the treatment of Type 2 Diabetes Mellitus. In addition to their potential as inhibitors for Type 2 Diabetes Mellitus, these natural bioactive compounds also offer the advantage of being easily accessible and affordable. This could be especially beneficial for patients in developing countries where access to expensive synthetic drugs may be limited. However, before these compounds can be utilized as therapeutics, extensive clinical trials and studies are necessary to determine their optimal dosage, potential drug interactions, and long-term effects. Nonetheless, the promising properties of these compounds make them a worthwhile avenue for future research and development in the field of diabetes treatment.

CONCLUSION

Cyanobacteria constitute a unique group of oxygenic photosynthetic bacteria and populate diverse habitats throughout the world. Their potential as a good source of new therapeutic lead compounds has been realized during the past two decades, as several bioactive molecules obtained from cyanobacteria show a broad spectrum of activities, such as antitumor, antibacterial, and antiviral effects, antioxidant, anti-inflammatory and protease inhibition. As Diabetes Mellitus is rising at alarming epidemic level throughout the world, effective drugs with low or no toxicity need to be developed. And one such way for it is the use of natural bioactive compounds which will have least side effects.

From the *insilico* study, it is suggested that the natural bioactive compounds of cyanobacterial strains and from other natural sources is the binding energy determines the strength of interaction between a ligand and an enzyme. The lowest binding energy is the outcome of the best binding conformer at its receptor site or active site of an enzyme (Xu *et al.,* 2008). The docked ligands displayed acceptable binding energy values for G-6-P (Glucose-6-Phosphatase) and GSK-3β (Glycogen Synthase Kinase-3β). These results suggest that Cyanobacterial and other natural bioactive compounds such as Antillatoxin B, Bastadin, Lyngbyatoxin A, Curacin D, could serve as inhibitor for T2DM. Demonstrated potential binding energy towards the specific target protein, **G-6-P (Glucose-6-Phosphatase) and GSK-3β (Glycogen Synthase Kinase-3β)** and thus, can be a potential target to develop drugs that can interact and control T2DM.

Further research is needed to determine the effectiveness and safety of these natural bioactive compounds as inhibitors for T2DM. Additionally, exploring their potential as drug candidates could lead to the development of more targeted and effective treatments for T2DM. By understanding the mechanisms by which these natural bioactive compounds interact with G-6-P and GSK-3β, scientists can potentially design drugs that specifically target these proteins to regulate glucose metabolism in individuals with T2DM. This targeted approach could minimize side effects and improve overall treatment outcomes. However, rigorous clinical trials and extensive research are necessary to ensure the safety and efficacy of these compounds before they can be utilized as potential treatments for T2DM.

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