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Quantitative Structure Activity Relationship (QSAR) Study of Antidiabetic Drugs: A Review

Saumya Darshana Shikha[1], Sahib Singh[1], Pankaj Wadhwa[1], Sanjeev K. Sahu[1]*

[1]Department of Pharmaceutical Chemistry, Lovely Professional University, Phagwara, Punjab, 144411 INDIA

Abstract:

In current scenario, Quantitative Structure Activity Relationship (QSAR) is most commonly used to design and develop new compounds. This method has advantage to predict the biological potency of designed compounds on the basis of available structural data with their biological activity profile. QSAR mainly involves the use of various statistically parameters, and ultimately reduce the cost & time to found new potent compounds. This review article mainly focused to summarize the QSAR study on different antidiabetic drugs.

Keywords: QSAR, Diabetes mellitus, Antidiabetic drug, Drug Design

***Corresponding author details:**

Sanjeev Kumar Sahu,

Department of Pharmaceutical Chemistry, Lovely Professional University, Phagwara, Punjab, INDIA 144411

Email: sanjeevsahu82@yahoo.co.in, Contact No. : +91-9993406614

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1. INTRODUCTION

Diabetes mellitus (DM) is form of endocrine metabolic disorder in which amount of blood sugar in the body is increased. There are two mechanisms that can cause diabetes: A) Inadequate insulin production, B) Poor insulin sensitivity to beta cells. As per Ancient Hindu Physician 'Madhumeha' is a disease wherein quiet passes sweet urine and shows sweetness everywhere throughout the body [1].

Presently, T2DM disturbs over 300 million individuals in the world and thus creates a serious worldwide health load [2]. Individuals more than 70 years having type 2diabetes have just double probability of dementia as compare to without type 2 diabetes peoples [3]. The quantity of persons with type 2 DM is rising in every country with 80% of people with DM living in low and middle salary countries. Despite the fact that T2DM is broadly detected in adults, its occurrence has significantly improved over the past two decades in the pediatric age group [4].

It is predictable that in the world, there are 415 million people having diabetes which is evaluated to be 1 in 11 of the world's grown population. There are 46% of individuals with diabetes which are not diagnosed. The figure is expected to growth to 642 million people existing with diabetes global by 2040.

Figure 1: Diabetes cases in different countries

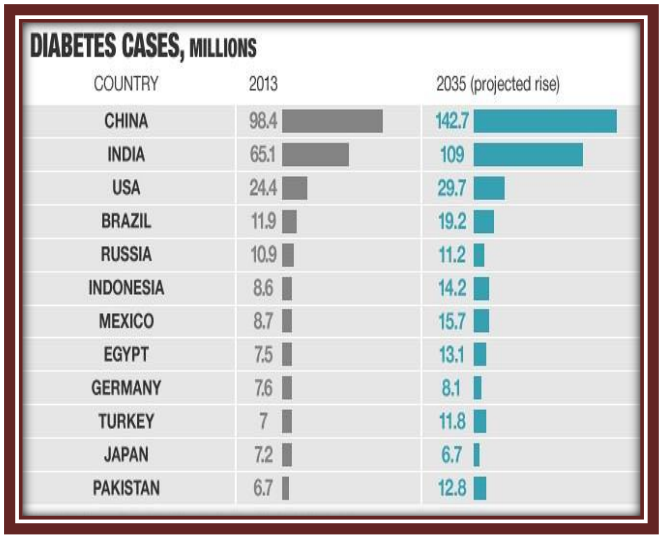
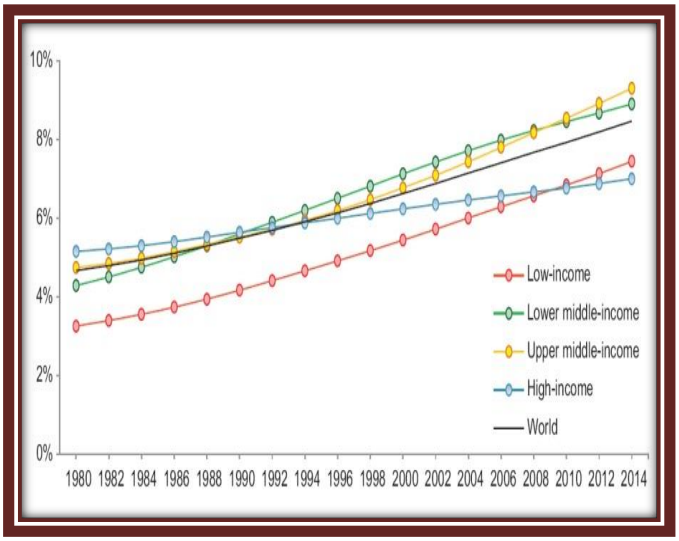


Figure 2: Diabetes cases related to income of people



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2. CLASSIFICATION OF DIABETES MELLITUS

The diabetes mellitus are categorized as Type 1 diabetes mellitus and Type 2 diabetes [5-7].

Type 1 DM is generally called insulin dependent diabetes. It is immune system issue. Insulin conveying cells in the pancreas are decimated thus there is almost no generation of insulin. Type1 is assumed to be brought about by a mix of genetic weakness and natural variables. Yet appropriate reason is not clear.

Type 2 DM is non-insulin dependent diabetes. The beta cells become invulnerable toward insulin, and then pancreas can't provide sufficient insulin as conquest of its opposition. It origins genuine medical problems, for example, cardiovascular illness, unexpected passing, visual impairment, kidney disappointment, removals, breaks, feebleness, sadness, and subjective decay. It is gradually normal, basically in view of increments in the ubiquity of a stationary way of life and corpulence. Medicines can be exercise, drug and insulin treatment [4].

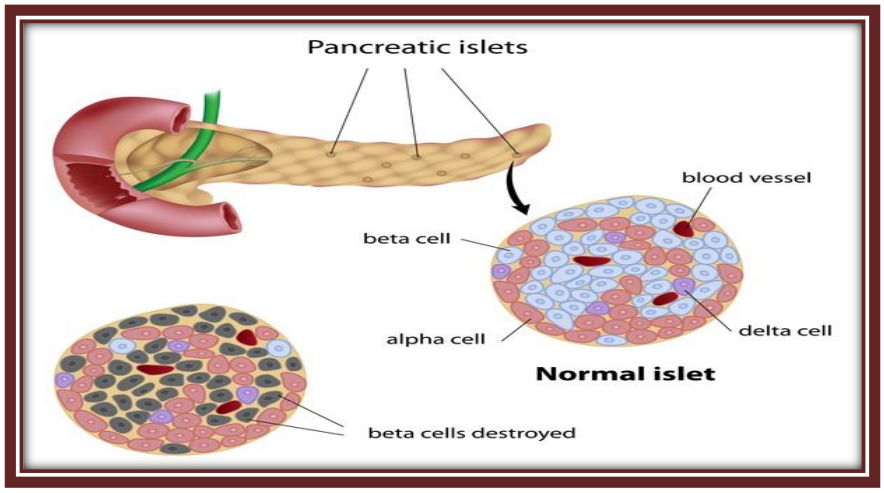

Figure 3: Representation of Type 1 Diabetes Mellitus

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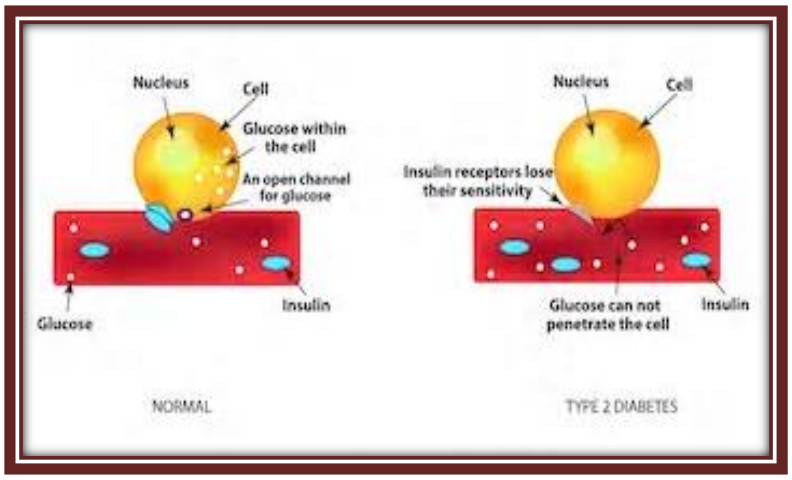
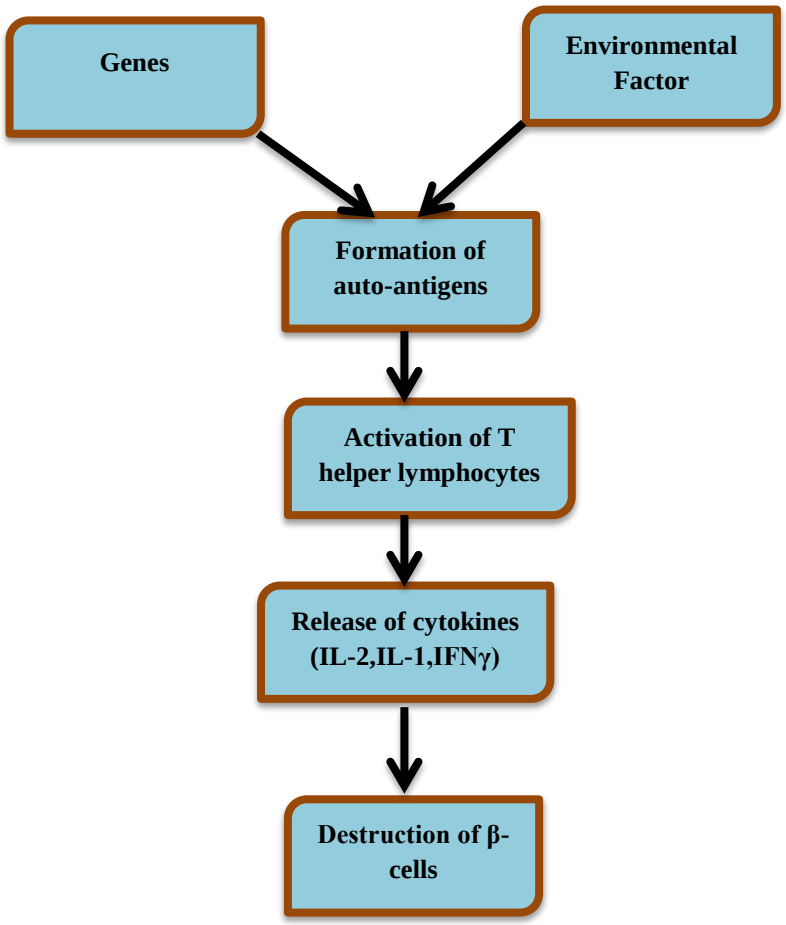


Figure 4: Representation of Type 2 Diabetes Mellitus

3. PATHOGENESIS OF TYPE 1 AND TYPE 2 DM

Pathogenesis of Type1 and Type2 DM was explained schematically in figure 5 and figure 6:



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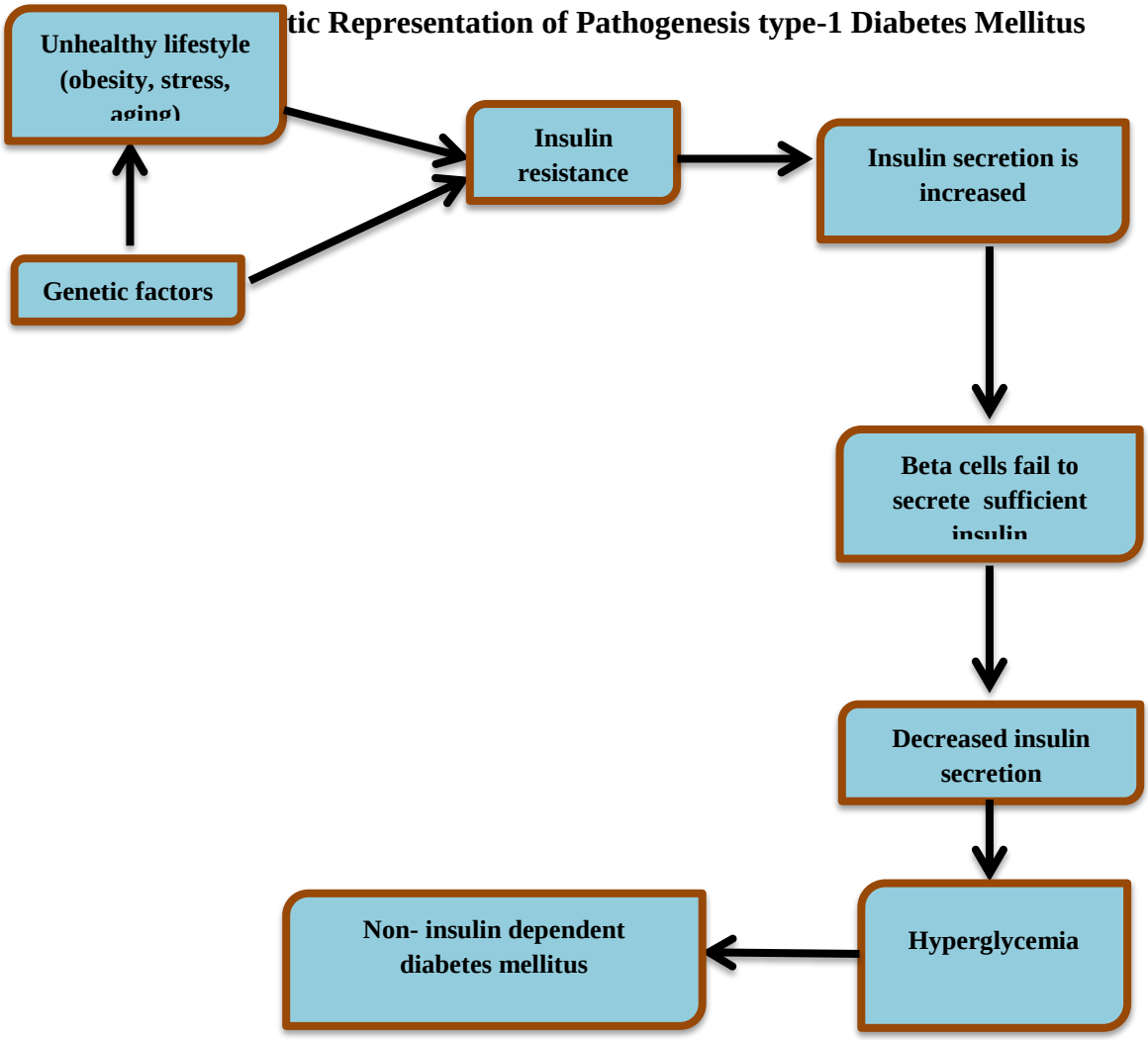

Figure 6: Systematic Representation of pathogenesis of type 2 diabetes mellitus

4. QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP (QSAR) STUDY

Chemistry has a significant impact in depicting the conduct display of chemical compounds. Developments of methods lead to adjustment of the chemical features of molecules which highlights the compounds in the field of chemistry as well as in the different fields of natural sciences [8].

QSAR is a system that endeavors to predict the movement, reactivity, and properties of an obscure arrangement of atoms dependent on investigation of a condition relating the structures of

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particles to their separate estimated action and property. QSAR method depend upon basic science guideline that expresses that the natural action of any ligand or compound is connected with the arrangement of atoms forming the molecular structure. As it were, basically related particles have comparable biological activities. This basic proof can be characterized as far as a progression of factors called molecular descriptors. In QSAR, the natural action is meant as an element of these molecular descriptors as delineated in Equation given beneath;

Biological response or activity = (f molecular descriptors)…….

The model consequently created dependent on the natural exercises of realized ligands is utilized to anticipate the reaction of new mixes. QSAR examines hence incorporate determination of dynamic and latent mixes with the degree of their natural action, depiction and estimation of sub-atomic portrayal and computation of sub-atomic descriptors, choice of proper sorts pursued by development of the numerical model and its evaluation [9].

The model consequently created dependent on the biological activities of realized ligands is utilized to anticipate the reaction of new compounds. QSAR studies hence incorporate determination of active and inactive compounds with the degree of their biological action, depiction and estimation of molecular portrayal and computation of molecular descriptors, choice of proper sorts pursued by development of the numerical model and its evaluation [10].

The QSAR examination is transcendently planned at measurement of compound proof pursued by building up a reasonable useful relationship tending to a given reaction. The separated compound or physicochemical proof can be worked for alteration of chemical structures prompting the 'fine-tuning' of the properties and biological activity, e.g., diminished lipophilicity, improved movement, and diminished toxicological appearance. In this manner, arithmetic here helps as an actualize for determining a reasonable relationship which is then exploited according to the need of the designer. On an a lot more extensive point of view, QSAR thinks about joins roads of science and material science representing inborn sub-atomic nature, arithmetic and insights for displaying and count, and science to include the included biochemical connection. In this manner, predictive numerical models are created investigating the information on science and science in a judicious manner to meet the ideal need of the synthetic substances [11]. Various ideas and viewpoints of science are implicitly utilized so as to determine prescient QSAR models that might be utilized for forecast of endpoint information of an enormous

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quantity of untested synthetic compounds. It may be imagined that the job of science in QSAR examination is to give a dynamic spine to building up a trademark connection among's science and science of the researched synthetic substances [8-11].

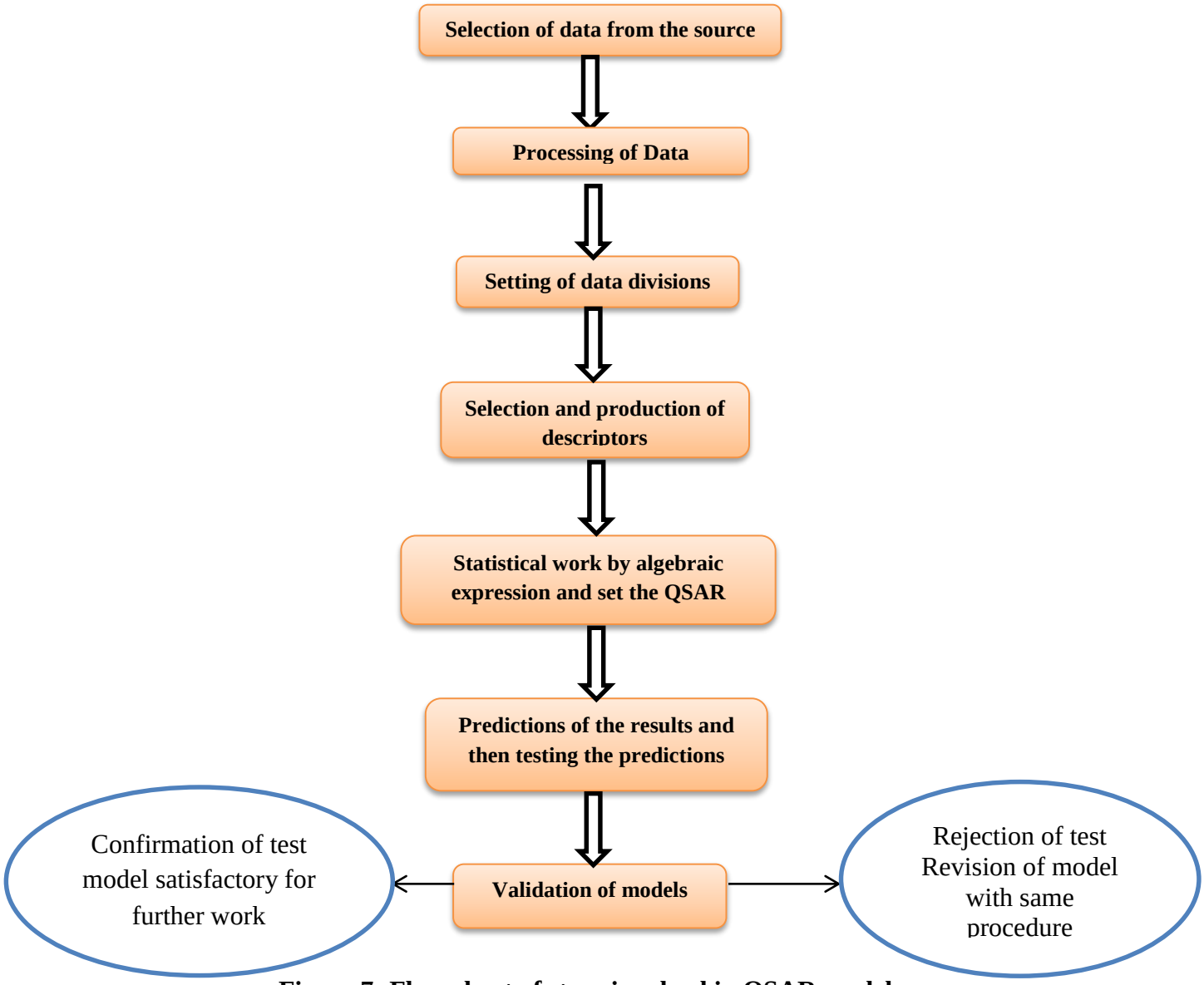

Figure 7: Flow chart of steps involved in QSAR model

Objectives of QSAR study

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- QSAR is used to correspond structural, statistical, chemical and physical properties with biological activity by different approaches.
- QSAR model is logical believable tools for foreseeing and arranging biological activities untested synthetic substances.
- QSAR is an important method for lead development (improvement)
- It is used in drug discovery process as a screening and enhancement method to terminate from advancement those synthetic substances lacking "drug like" characteristics or those chemicals anticipated to evoke a poisonous reaction.

5. QSAR Study of Antidiabetic Drugs :

Number of the literature reported on QSAR study of antidiabetic drugs and among these some important were discussed as follow:

Dixit et al., 2008 reported QSAR study on certain PPAR-gamma agonists utilizing TATA-BioSuite software to recognize the fundamental structure related physicochemical highlights. There were selected 18training set and 5test set from the entire compounds using k-nearest neighbor (kNN) clustering. Peroxisome proliferator-activated receptors are a gathering of nuclear receptors that play an important part in the lipid metabolism and its storage. Thiazolidinediones (TZDs), are significant compounds which are utilized in the treatment of Diabetes mellitus and other diseases which characteristic the insulin opposition. These mediators markedly raise sensitivity of insulin within different tissues that results to reduce the raised plasma glucose level. PPAR-gamma agonists have been created to defeat the issue related with TZDs (like lethality) and utilized as a potential Anti-Diabetic specialists. A reasonable method to create high quality predictive models can be based on linear free energy with the help of QSAR [12]**.**

Zhi et al., 2015 designated six SGLT-2 inhibitors with anthyperglycemic activity to develop 3D-QSAR utilizing CoMFA and CoMSIA models. An arrangement of 39 established compounds was utilized to develop the models, and then assessed by progression of interior and outer cross-approval systems. SGLT2 inhibitors explicitly target renal glucose transporters and don't straightforwardly affect islet, in this way leaving the insulin emission work absolutely unblemished without upsetting the counter administrative hormones. There are various SGLT-2

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forced for the administration of T2DM, containing: Canagliflozin, Dapagliflozin, Luseogliflozin, Empagliflozin , Sergliflozin etabonate etc. The 3D-QSAR models were used to look at basic prerequisites for refining power of triazole subsidiaries as SGLT -2 inhibitors. These models are utilized to plan & expect the SGLT inhibitory action of recently structured compounds [13]**.**

Rathi et al., 2004 finished the recognizable proof of Pharmacophore and three dimensional quantitative structure–action contemplates on a lot of N-(2-Benzoylphenyl)- l-tyrosine for their PPAR-gamma agonist action using logico-auxiliary based programming. An aggregate of 23 molecules having a place with three fundamental models were disseminated into a preparation set and test set of three compounds. There were two different 3D-QSAR models which relate the properties with appropriations of primary and secondary biophoric destinations. These models were also demonstrated the decent connection between watched & anticipated action in preparing and test set both. Along these lines might be advantageous in structuring novel substance elements as PPAR-gamma agonists [14]**.**

Ibrahim et al., 2018 displayed to examine the antidiabetic exercises of twenty seven Oxadiazoles subclasses. The improvement with antidiabetic agents were achieved utilizing Density Functional Theory strategy using B3LYP adaptation with 6-31G premise set. Hereditary Function Algorithm was utilized to frame four different models. An enormous number of compounds containing 1, 3, 4-oxadiazole nucleus were reported to treat T2DM by hindering α-glucosidase. The QSAR study data is basically related with molecular docking results which play as important tool to design new potent antidiabetic compounds with improved movement against alpha-glycosidase [15]**.**

Liu et al., 2018 depicted Xanthones and their derivatives to display robust inhibitory exercises toward α-glucosidase, a compound that is engaged with Modern sicknesses, for example, Diabetes, HIV, and diseases. Xanthones signify a class of normally happening exacerbates that are comprehensively dispersed in nature and display numerous pharmacological properties, for example, antioxidant, antimalarial and anti-inflammatory actions, restraint of an assortment of tumor cell lines' development, and balance of PKC isoforms. Solid QSAR model has been successfully perceived by utilizing MLR for 34 xanthone derivatives having inhibitory exercises toward α-glucosidase [16].

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Jiang et al., 2012 concentrated on the study of the 3D structural requirements for the high potent biological activity of dipeptidylpeptidase (DPP) IV's inhibitor. At first, Molecular dynamic and mechanic simulations study were performed and found the conformations of the potent DPPIV's inhibitor. The 3D QSAR study was completed for arylmethylamine DPP-IV inhibitors with CoMFA approach using MD/MM-determined molecular conformers as templates. There are several studies that have confirmed that the amount of circulating GLP-1 is increased to improve the production of insulin in the body through inhibition of DPP IV. Accordingly, it has significant role as favorable approach to design some potent drugs for type2 diabetes. The prediction of arylmethylamine analogs by 3D-QSAR model is the main global purpose of this effort [17]**.**

Thareja et al., 2010 studied on Thiazolidinedione (TZDs) to treat diabetic patients that is used to adverse insulin resistance by activation of PPAR-γ. For the improvement and optimization of lead, Self-Organizing Molecular Field Analysis (SOMFA) has been carried out on TZD scaffold having h-PTP1B inhibitory actions. Protein tyrosine phosphatase1B (h-PTP1B) is a main non trans-membrane phospho-tyrosine phosphatase in human tissues. The insulin sensitivity would be increased by opposing h-PTP1B inhibitors [18]**.**

Karim et al., 2018 carried out the 2D and 3D QSAR of tetralin-sulfonamide derivatives as anti-diabetic and dipeptidyl peptidase-IV (DPP-4) inhibiting agents using auto QSAR of Schrodinger. Three were all the designed new compounds given significant experimental data representing considerable connection between alignment-independent descriptors, electrostatic and steric field descriptors with the anti-diabetic activity. The DPP-4 enzyme catalyzes the N-terminal dipeptides of glucagon-like peptide-1 that have important role to control the blood glucose level. Therefore, it acts as key target for the treatment of type 2 diabetes [19]**.**

Liang et al., 2011 reported the receptor-based CoMFA and CoMSIA methods to examine the QSAR among 106 PT equivalents. Pentacyclic triterpenes (PT) are found in the nature and were identified as glycogen phosphorylases in the treatment of type-2 diabetes. In this study, the completion of QSAR study of PT as GPb inhibitors has been done and designed 56 compounds based on the QSAR model [20].

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Saqib et al., 2009 performed 3D quantitative structure–activity relationship (3D-QSAR) compressing CoMFA and CoMSIA on 45 triazolopiperazine amide derivatives as DPP-IV inhibitors. GLP-1 is an insulinotropic hormone which has multi-effects like glucose-dependent stimulation of insulin and inhibition of glucagon secretion, inhibition of gastric emptying and the reduction of appetite. However, GLP-1 is rapidly inactivated by the serine peptidase or DPP-IV. In this study, the anti-diabetic activities of triazolopiperazine amide derivatives were done by 3D CoMFA and CoMSIA QSAR analyses. With the help of CoMFA and CoMSIA contour maps, the explanations of steric effects, electrostatic effects, hydrophobic effects and hydrogen bond acceptor fields effects around the aligned molecules on their activities were done [21]**.**

Sharma et al., 2018 performed 3D-QSAR CoMFA and CoMSIA studies for the trifluorophenyl derivatives as DPP IV inhibitors. The main purpose of this study is to create a model that establishes a useful approach for the design of new inhibitors of DPP-IV with potential anti-diabetic activity. There are some beneficial evidences for the structural modification of these inhibitors basis on the resulting QSAR models from this study [22].

Kesar et al., 2016 investigated the best QSAR model with left of adept and important descriptors like electronic, lipophilic and topological, using multiple linear regression (MLR) and partial least square (PLS), model further elucidated by using forward feed neural network analysis (FFNN). Glycogen synthase kinase (GSK) is a multi-targeted serine/threonine kinase, originally recognized as an enzyme, having two identical isoforms namely GSK-3α (51kDa) and GSK-3β (47kDa). For the treatment of type II diabetes, there are numerous GSK-3β small molecule inhibitors in clinical trials. The model discloses that total dipole moment, bond dipoles and kappa 3 are requirement descriptors for defining further promising GSK-3β antagonist with high and accountable potency against target [23].

Vitthal et al., 2016 reported a series of cyanopyrrolidines as Type II anti-diabetic agents using 3D-QSAR to explain the three dimensional structural features which are vital for the Type II anti-diabetic activity. The results variety from 3D QSAR can give important information regarding the structural characteristics which are providers of the inhibitory potency of cyanopyrrolidines. In addition, pharmacophore modeling was utilized to identify the structural

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characteristics of the cyanopyrrolidines which are vital for the biological activity of the compounds. On the basis of these results can provide some important information for further development of new potent DDP-IV Inhibitors for the treatment of diabetes [24].

6. CONCLUSION

Apart from broad range of application, QSAR study has found it potential in drug designing. Guidelines for validation, development and application of QSAR study are discussed and can be summarized to develop a predictive QSAR model.

As per given examples in literature review, it has been studied using QSAR to analyze properties and biological activities of compounds with the help of different types of software to predict a QSAR model. I would like to extend it to study QSAR on different Coumarin (secondary metabolites) derivatives to find out its properties, reactivity and biological activity which will help in treatment of T2 DM.

So in further study, I would like to work on reporting different types of predictive QSAR model of these drugs to overcome insulin resistance using QSAR study at laboratory scale.

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