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(RESEARCH ARTICLE)

Comparative assessment of physicochemical properties of plant active molecules having antidiabetic potential

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Abstract

Diabetes mellitus is one of the most prevalent diseases found in all parts of the world. It is a complex heterogeneous group of metabolic disorders including hyperglycemia and is associated with imbalances in carbohydrate, protein, and lipid metabolism. The management of diabetes mellitus is considered a global problem. In current allopathic therapy, oral hypoglycaemic agents and insulin are used to control diabetic conditions. Traditional herbal drugs with multiple phytoconstituents and properties have been used as medicines for the treatment of a wide range of diabetes. Herbal medicines have been intrinsically safe, due to their natural occurrence, efficacy, and fewer side effects. The active molecules present in different phytoconstituents of herbal medicines act by different mechanisms to reduce the amount of glucose level in the blood. The functional efficiency of these active molecules largely depends on their physicochemical properties. In the present study, the physicochemical properties of important plant active molecules are analyzed and assessed which have antidiabetic potential and are particularly involved in regeneration of pancreatic β-cells.

Keywords: Phytochemicals; Active molecules; Antidiabetic; Physicochemical properties; Bioactivity

1. Introduction

Traditional herbs and phytochemicals have been used as medicines since ancient times for the treatment of a wide range of diseases [1, 2]. Due to their natural occurrence, good efficacy, non-toxic, fewer side effects, and much cheaper alternatives than synthetic drugs, these herbal medicines are excellent candidates for oral therapy [3]. Diabetes mellitus is a complex metabolic disorder resulting from either insulin insufficiency or insulin dysfunction [4, 5]. Phytochemicals are reported and proven to have a major role in the management of diabetes [6, 7]. Several types of phytoconstituents such as alkaloids, glycosides, flavonoids, polysaccharides, glycolipids, peptidoglycans, saponins, and others have been reported as potent antidiabetic agents. The use of these phytoconstituents may delay the development of complications due to diabetic conditions and may regulate and control metabolic abnormalities through a variety of mechanisms [8]. The active molecules of these phytochemicals are believed to ameliorate diabetic syndromes through different mechanisms of action [9, 10]. The active molecules may enhance insulin secretion by activating β-cell and sensitivity, glucose uptake by adipose tissues, inhibiting glucose absorption from the intestine and glucose production from hepatocytes, and may increase its oxidation. Further, the molecular mechanism of these phytochemicals active molecules also varied to treat diabetes mellitus.

Largely these phytochemicals are secondary metabolites of plants. Secondary metabolites are low molecular weight chemical compounds which produced as families of related compounds [11, 12, 13]. Secondary metabolites are

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specialized metabolites that provide a selective advantage for the organisms, especially during adverse ecological conditions by increasing their survivability or fecundity [12, 13]. There are four different classes of plant secondary metabolites: terpenoids, phenolic compounds, alkaloids, and sulfur-containing compounds. Secondary metabolites are the product of primary metabolites. They are produced from biosynthesis modifications, such as methylation, glycosylation, and hydroxylation [12, 13]. Relatively, secondary metabolites have a more complex structural composition, and other side chains compared to primary metabolites [14]. The structural features of secondary metabolites are an important aspect of understanding the relationship between their molecular structures and biological or pharmacological activities.

Phytochemical compounds with different structures but with the same therapeutic activity act as active moieties for the treatment of various diseases. Phytochemicals and their active molecules exhibit a staggering variation and diversities in their chemical structures, properties, and biological activities [15, 16]. In the present study, attempts have been made to evaluate the physicochemical properties of plant active molecules present in phytochemicals that are proven to have antidiabetic properties. The structural and chemical features of phytochemical active molecules are accountable for delivering a variety of characteristics including therapeutic applications, and the solubility, and stability of the molecules [17]. Hence the knowledge about characteristic physiochemical properties of phytochemical active molecules will be useful to understand the relations between their molecular properties and biological activities that are attributed to being responsible for their characteristic antidiabetic properties [18].

2. Materials and Methods

The structural information of phytochemical active molecules was searched and obtained from 'PubChem' (https://pubchem.ncbi.nlm.nih.gov/) chemical database [19] by mapping to chemical identifiers. Further, the canonical "Simplified Molecular Input Line Entry System" (SMILES) of each active molecule was also generated from PubChem (https://pubchem.ncbi.nlm.nih.gov/) database.

The web-based tool SwissADME (http://www.swissadme.ch/) [20] was used to compute the basic physicochemical properties of phytochemical active molecules. To assess the drug-likeness of the active molecules, multiple scoring schemes and properties namely, Lipinski's rule of five (RO5), Ghose filter, Number of Leadlikeness violations, and weighted quantitative estimate of drug-likeness (QEDw) were calculated and analyzed. The active molecules were screened based on Lipinski's 'Rule of Five' and assessed for ADMET properties.

3. Results and Discussion

In the present study, we targeted to evaluate and delineate the physicochemical properties of some important phytochemical active molecules that are reported to have therapeutic potential against diabetes. These active molecules have a specific physiological role in the regeneration of pancreatic β cells (Table 1) and help to combat diabetic conditions through different mechanisms [21, 22, 23, 24]. Such as Aegelin, Marmesin, Marmelosin, Andrographolide, Trigonellin, and Fenugreekine acts through the increase in insulin secretion, while Catharanthine, Vindoline, Vinblastine, and Vincristine act to control the release of insulin. Similarly, Gymnemic acid, Stigmasterol, and Betaine act through the inhibition of α-glucosidase. Another important active molecule Ginsenosides acts as scavengers of free radicals (Table 1). These phytochemical active molecules were mapped to chemical identifiers employed by standard chemical databases 'PubChem' database to retrieve their 2D chemical structures (Figure 1) and SMILE formulae (Table 1). These SMILE formulae were further used for downstream analyses and studies of the physiochemical properties of these phytochemical active molecules.

Table 1 List of phytochemical active molecules targeted in this study

Active Molecule	PubChem ID	Mechanism of action	Canonical SMILES
Aegelin	15558419	Insulin secretion	COC1=CC=C(C=C1)C(CNC(=O)C=CC2=CC=CC=C2)O
Marmesin	334704	Insulin secretion	CC(C)(C1CC2=C(O1)C=C3C(=C2)C=CC(=O)O3)O
Marmelosin	10212	Insulin secretion	CC(=CCOC1=C2C(=CC3=C1OC=C3)C=CC(=O)O2)C
Ginsenosides	3086007	Free radical scavenging	CC(=CCCC(C)(C1CCC2(C1CCC3C2(CCC4C3(CCC(C4(C)C)O)C)C)C)O)C
Catharanthine	5458190	Insulin releaser	CCC1=CC2CC3(C1N(C2)CCC4=C3NC5=CC=CC=C45)C(=O)OC

Vindoline	260535	Insulin releaser	CCC12C=CCN3C1C4(CC3)C(C(C2OC(=O)C)(C(=O)OC)O)N(C5=C4C=CC(=C5)OC)C
Vinblastine	13342	Insulin releaser	CCC1(CC2CC(C3=C(CCN(C2)C1)C4=CC=CC=C4N3)(C5=C(C=C6C(=C5)C78CCN9C7C(C=CC9)(C(C(C8N6C)(C(=O)OC)O)OC(=O)C)CC)OC)C(=O)OC)O
Vincristine	5978	Insulin releaser	CCC1(CC2CC(C3=C(CCN(C2)C1)C4=CC=CC=C4N3)(C5=C(C=C6C(=C5)C78CCN9C7C(C=CC9)(C(C(C8N6C=O)(C(=O)OC)O)OC(=O)C)CC)OC)C(=O)OC)O
Andrographolide	5318517	Insulin secretion	CC12CCC(C(C1CCC(=C)C2CC=C3C(COC3=O)O)(C)CO)O
Trigonellin	5570	Insulin secretion	C[N+]1=CC=CC(=C1)C(=O)[O-]
Fenugreekine	444170	Insulin secretion	C1=CC(=NC(=C1)C(=O)N)C2C(C(C(O2)COP(=O)(O)OP(=O)(O)OCC3C(C(C(O3)N4C=NC5=C(N=CN=C54)N)O)O)O)O
Gymnemic acid	11953919	α-glucosidase inhibitor, insulin secretion	CC=C(C)C(=O)OC1C(C2(C(CC1(C)C)C)C3=CCC4C5(CCC(C(C5CCC4(C3(CC2O)C)C)(C)CO)OC6C(C(C(C(O6)C(=O)O)O)O)O)C)COC(=O)C)O
Stigmasterol	5280794	α-glucosidase inhibitor, insulin secretion	CCC(C=CC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C
Betaine	247	α-glucosidase inhibitor, insulin secretion	C[N+](C)(C)CC(=O)[O-]

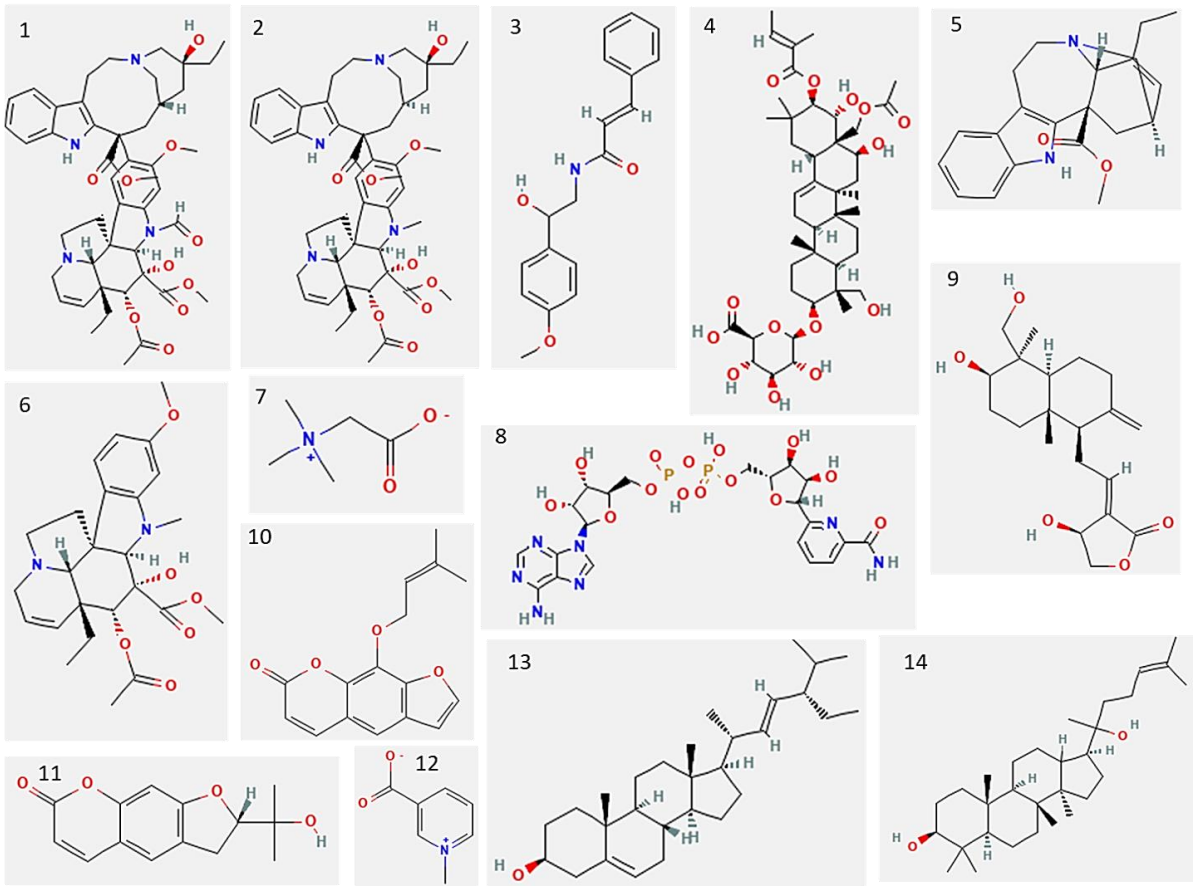

Figure 1 (1 to 14) 2-D structures of phytochemical active molecules Vincristine, Vinblastine, Aegeline, Gymnemic acid, Catharanthine, Vindoline, Betaine, Fenugreekine, Andrographolide, Marmelosin, Marmesin, Trigonelline, Ginsenosides, and Stigmasterol respectively

3.1. Evaluation of Drug-likeness Properties

Analysis and evaluation of the drug-likeness properties of a prospective chemical compound is crucial to assess its therapeutic potential [25]. Parameters like logP, MW, number of hydrogen-bond acceptors (HBA), number of hydrogen-bond donors (HBD), MLOGP, WLOGP, MR, and number of atoms are important attributes to evaluate drug-likeness properties. SwissADME was used to calculate drug-likeness properties for each active molecule by applying Lipinski's rule of five (RO5) and Ghosh filter. As per Lipinski's rule of five (RO5), a potential drug-like compound should have a molecular weight (MW) ≤ 500 Da, hydrogen bond donor (HBD's) ≤ 5, hydrogen bond acceptor (HBAs) ≤ 10 and (log P) ≤ 5 (Lipinski 2004). However, out of the above five criteria, one violation may be allowed. Out of fourteen, eight active molecules passed Lipinski's filter without any violation, while two molecules passed with one violation. Six out of these eight also passed Ghosh Filter without any violations. Thus Aegelin, Marmesin, Marmelosin, Catharanthine, Vindoline, and Andrographolide showed drug-likeness properties. The results of the drug-likeness of all active molecules are shown in Table 2.

Table 2 Durg-likeness properties of phytochemical active molecules

Active Molecule	A	B	C	D	E	F	G	H	I	J	K
Aegelin	297.35	0.17	7	3	86.10	58.56	2.44	-3.16	0	0	0.55
Marmesin	246.26	0.36	1	4	67.45	59.67	1.91	-2.92	0	0	0.55
Marmelosin	270.28	0.19	3	4	77.50	52.58	3.50	-4.00	0	0	0.55
Ginsenosides	444.73	0.93	4	2	138.72	40.46	8.54	-7.71	1	3	0.55
Catharanthine	336.43	0.48	3	3	102.27	45.33	2.80	-3.76	0	0	0.55
Vindoline	456.53	0.60	6	7	128.42	88.54	1.50	-3.35	0	0	0.55
Vinblastine	810.97	0.59	10	11	232.52	154.1	3.88	-6.84	2	3	0.17
Vincristine	824.96	0.57	11	12	233.11	171.17	3.13	-6.39	2	3	0.17
Andrographolide	350.45	0.75	3	5	95.21	86.99	2.16	-3.18	0	0	0.55
Trigonellin	137.14	0.14	1	2	35.05	44.01	0.51	-1.39	0	4	0.55
Fenugreekine	663.43	0.48	11	18	140.12	346.89	-5.92	0.25	3	4	0.11
Gymnemic acid	806.98	0.84	10	14	207.11	229.74	3.86	-6.62	3	3	0.11
Stigmasterol	412.69	0.86	5	1	132.75	20.23	8.56	-7.46	1	3	0.55
Betaine	117.15	0.80	2	2	28.35	40.13	-0.13	-0.35	0	4	0.55

Details of columns

A	Molecular weight	G	XLOGP3
B	Fraction Csp3	H	ESOL Log S
C	Number of rotatable bonds	I	Lipinski violations
D	Number of H-bond acceptors	J	Ghose violations
E	MR	K	Bioavailability Score
F	TPSA		

The bioavailability properties of active molecules may be analyzed and inferred by the bioavailability RADAR plot (Figure 2). The pink area in the RADAR plot shows the most favorable zone for each of the bioavailability properties. Table 2 clearly shows that out of fourteen targeted active molecules, ten fulfilled the recommended molecular size (≤ 500 g/mol) by Lipinski for a good drug candidate, except Vinblastine, Vincristine, Fenugreekine, and Gymnemic acid for which the estimated size is 810.97, 824.96, 633.43 and 806.98 g/mol, respectively. Total Polarity Surface Area (TPSA) is an important attribute in assessing the polarity (POLAR) of active molecules. The recommended range of TPSA is 20 – 130 $Å^2$ for a molecule to be a good drug candidate. Again, except Vinblastine, Vincristine, Fenugreekine, and Gymnemic acid, the TPSA values of the rest of the active molecules are calculated within the range of 20 – 90 $Å^2$ (Table 2). The number of rotatable bonds in a molecule is used to evaluate the flexibility (FLEX) property. Except for Vinblastine, Vincristine, Fenugreekine, and Gymnemic acid, all the targeted active molecules are having the number of rotatable bonds ≤ 7 (tolerable range ≤ 9) (Table 2). Lipophilicity is an important feature that shows the capacity of permeability of a molecule across the cell membrane [26, 27]. The Lipophilicity (LIPO) of a molecule is evaluated using XLOGP3. The

calculated XLOGP3 value for most of the targeted active molecules fall within the recommended range from – 0.7 to + 5.0, except Ginsenosides and Stigmasterol which suggest a good permeability and absorption of the targeted molecules across the cell membrane (Table 2). Further, the insolubility of a molecule is another important parameter influencing the absorption of phytochemicals in any formulation process. Insolubility (INSOLU) of the targeted active molecules was evaluated using ESOL (log S) for which the recommended ranges are 'Insoluble < -10 < Poorly < -6 < Moderately < -4< Soluble < -2 Very < 0 < Highly'. The calculated ESOL (log S) value suggests that Ginsenosides, Stigmasterol, Vinblastine, Gymnemic acid, and Vincristine are poorly soluble, while the rest of the other active molecules are predicted to be soluble (Table 2). The insolubility of these compounds may be due to their high molecular weight. The Unsaturation (INSATU) is another important parameter which was determined using 'Fraction Csp3'. The recommended range for 'Fraction Csp3' is between 0.5 to 1. The predicted value of 'Fraction Csp3' for Vincristine, Vinblastine, Vindoline, Andrographolide, Betaine, Gymnemic acid, Stigmasterol, and Ginsenosides are between 0.5 to 1 (Table 2). For the rest, it is less than 0.5. Interestingly most of the targeted phytochemical active molecules are predicted to have a bioavailability score equal to 0.55 (Table 2), except Vinblastine, Vincristine, Fenugreekine, and Gymnemic acid. That means these active molecules possess outstanding oral-bioavailability properties [28].

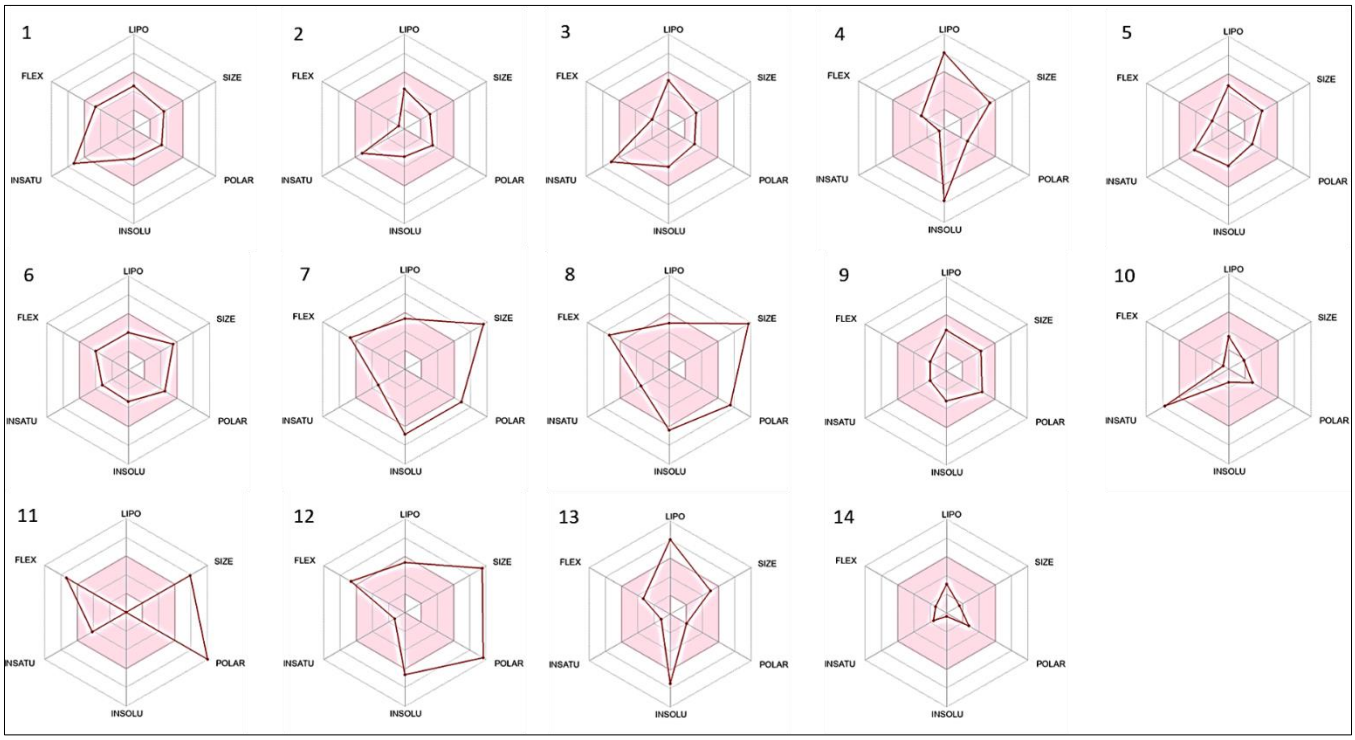

Figure 2 (1 to 14) Bioavailability Radar Plot of phytochemical active molecules Aegelin, Marmesin, Marmelosin, Ginsenosides, Catharanthine, Vindoline, Vinblastine, Vincristine, Andrographolide, Trigonellin, Fenugreekine, Gymnemic acid, Stigmasterol, and Betaine, respectively. The pink area inside each plot shows the optimal range for each property (Lipophilicity: XLOGP3 between − 0.7 and + 5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 Å2, solubility: log S not higher than 6, saturation: fraction of carbons in the sp3 hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds)

3.2. Evaluation of ADMET (absorption, distribution, metabolism, excretion and toxicity) properties

The study of pharmacokinetics parameters of active compounds is one of the important aspects to predict the therapeutic potential of phytochemicals [29, 30, 31]. The analyses of different attributes of pharmacokinetics parameters suggest that half of the targeted active molecules have high propensities for gastrointestinal (GI) absorption (Table 3), which means these molecules will easily be absorbed in the human intestine. Most of the targeted active molecules are predicted to have no ability to cross the blood-brain barrier (BBB permeant) (Table 3), except Aegelin, Marmesin, Marmelosin, and Catharanthine, suggesting there is no effect of these molecules on the central nervous system (CNS). The metabolic activities of phytochemicals active molecules were assessed with the potential of Cytochrome P450 inhibition. The predicted data (in Table 3) suggest that most of the targeted active molecules are non-inhibitors of all the CYP450. Further, the skin permeability coefficient (Kp) of the active molecules was also checked and calculated as prescribed by Potts and Guy (Potts and Guy, 1992). The log *K*p was predicted between − 14.55 to − 2.74 cm/s (Table 3). The more negative log *K*p corresponds to the less skin permeant the compounds.

Table 3 ADME properties of phytochemical active molecules

Active molecule	A	B	C	D	E	F	G	H	I
Aegelin	High	Yes	No	Yes	No	No	Yes	Yes	-6.38
Marmesin	High	Yes	No	Yes	No	No	No	No	-6.45
Marmelosin	High	Yes	No	Yes	Yes	Yes	No	No	-5.46
Ginsenosides	Low	No	No	No	No	No	No	No	-2.95
Catharanthine	High	Yes	Yes	No	No	No	Yes	Yes	-6.36
Vindoline	High	No	No	No	No	No	Yes	Yes	-8.02
Vinblastine	Low	No	Yes	No	No	No	No	Yes	-8.49
Vincristine	Low	No	Yes	No	No	No	No	Yes	-9.11
Andrographolide	High	No	Yes	No	No	No	No	No	-6.9
Trigonellin	High	No	No	No	No	No	No	No	-6.77
Fenugreekine	Low	No	No	No	No	No	No	No	-14.55
Gymnemic acid	Low	No	Yes	No	No	No	No	No	-8.48
Stigmasterol	Low	No	No	No	No	Yes	No	No	-2.74
Betaine	Low	No	Yes	No	No	No	No	No	-7.11

Details of columns

A	GI absorption
B	BBB permeant
C	Pgp substrate
D	CYP1A2 inhibitor
E	CYP2C19 inhibitor
F	CYP2C9 inhibitor
G	CYP2D6 inhibitor
H	CYP3A4 inhibitor
I	log Kp (cm/s)

4. Conclusion

The physicochemical properties of active compounds are important parameters during the bioprospection of phytochemicals and their constituents. Detailed analyses and assessment of physiochemical properties are required to predict the therapeutic potential of any active compounds. The targeted phytochemical active molecules in this study have great therapeutic potential against diabetes. The *in-silico* prediction and evaluation of these active molecules showed diversity in the properties of drug-likeness, ADME, and pharmacokinetics. Based on the overall criteria and physicochemical properties, Andrographolide and Trigonellin are predicted the best active molecules out of the targeted fourteen phytochemicals. The active pharmacological principle of Andrographolide and Trigonellin may use as oral drugs and act with low toxic risk via the topical route to help in the regeneration of pancreatic β cells. The above findings provide a strong basis for prospects and to further explore the deep insight into the mechanism of these important phytochemical active molecules.

Compliance with ethical standards

Disclosure of conflict of interest

All authors declare no any conflict of interest.

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