

**Table S1** Elements of the research question (What therapeutic targets have been used in *in silico* analyzes for the treatment of diabetes *mellitus*?) according to the PECo strategy (problem, exposure, and context) for systematic review.

Description	Abbreviation	Question elements
Problem	P	Therapeutic targets used in the treatment of diabetes <i>mellitus</i>
Exposure	E	Diabetes <i>mellitus</i>
Context	Co	<i>In silico</i> studies with molecular dynamics and/or molecular docking

**Table S2** Search equation for the databases used to include articles according to the eligibility criteria, aiming to answer the question: What therapeutic targets have been used in the *in silico* analyzes for the treatment of diabetes *mellitus*?

Database	Search equation
Medline (PubMed)	("therapeutic target" OR target OR treatment OR therapeutics) AND ("diabetes <i>mellitus</i> ") AND ("in <i>silico</i> " OR "computer simulation") AND ("molecular dynamics simulation" OR "molecular dynamic" OR "molecular docking simulation" OR "molecular docking")
Web of Science	("therapeutic target" OR target OR treatment OR therapeutics) AND ("diabetes <i>mellitus</i> ") AND ("in <i>silico</i> " OR "computer simulation") AND ("molecular dynamics simulation" OR "molecular dynamic" OR "molecular docking simulation" OR "molecular docking")
Scopus Filter used: Title/Abstract	('diabetes <i>mellitus</i> ') AND ('molecular dynamics simulation' OR 'molecular dynamic' OR 'molecular docking simulation' OR 'molecular docking')
Embase	'therapeutic target'/exp OR 'therapeutic target' OR target/exp OR target OR treatment/exp OR treatment OR therapy/exp OR therapy AND 'diabetes <i>mellitus</i> '/exp OR 'diabetes <i>mellitus</i> ' AND 'in <i>silico</i> analysis'/exp OR 'in <i>silico</i> ' OR 'computer simulation'/exp OR 'computer simulation' OR 'computer Model'/exp OR 'computer Model' AND 'molecular dynamics'/exp OR 'molecular dynamic' OR 'molecular docking'/exp OR 'molecular docking'
ScienceDirect Filters used: Research articles and Title, Abstract, Key Words	("diabetes <i>mellitus</i> ") AND ("in <i>silico</i> " OR "computer simulation" OR "molecular dynamics simulation" OR "molecular dynamic" OR "molecular docking simulation" OR "molecular docking")
Virtual Health Library Filters used: Title, Abstract, Key Words	("therapeutic target" OR target OR treatment OR therapeutics) AND ("diabetes <i>mellitus</i> ") AND ("in <i>silico</i> " OR "computer simulation") AND ("molecular dynamics simulation" OR "molecular dynamic" OR "molecular docking simulation" OR "molecular docking")

**Table S3** General characteristics of the structures of therapeutic targets *in silico* used in the included studies for the systematic review.

Therapeutic target	Experimental Data Snapshot			Homology Modeling
	PDB ID	Method	Resolution	Protein Sequence
<b>DPP-IV</b>	2ONC	X-Ray diffraction	2.55 Å	NA
	4A5S	X-Ray diffraction	1.62 Å	NA
	1R9N	X-Ray diffraction	2.30 Å	NA
	5Y7K	X-Ray diffraction	2.51 Å	NA
<b>GLP-1R</b>	3C5T	X-Ray diffraction	2.10 Å	NA
<b>PPAR<math>\gamma</math></b>	2PRG	X-Ray diffraction	2.30 Å	NA
	5TWO	X-Ray diffraction	1.93 Å	NA
	1I7I	X-Ray diffraction	2.35 Å	NA
<b>Akt</b>	3O96	X-Ray diffraction	2.70 Å	NA
	3QKM	X-Ray diffraction	2.2 Å	NA
	2UZS	X-Ray diffraction	2.46 Å	NA
<b>GLUT4</b>	NA	NA	NA	UNIPROT P14672
	4PYP	X-Ray diffraction	3.17 Å	NA
	5EQG	X-Ray diffraction	2.90 Å	NA
	3PCU	X-Ray diffraction	2.00 Å	NA
<b><math>\alpha</math>-amilase</b>	2QV4	X-Ray diffraction	1.97 Å	NA
<b>GLP-1</b>	3IOL	X-Ray diffraction	2.10 Å	NA
<b>GIP</b>	2QKH	X-Ray diffraction	1.90 Å	NA
<b>IR</b>	1IRK	X-Ray diffraction	2.10 Å	NA
<b>IRS1</b>	1IRS	Solution nmr	NA	NA
<b>GSK3<math>\beta</math></b>	1Q5K	X-Ray diffraction	1.94 Å	NA
<b>IGF1 and PI3K</b> (no information on the structure used)	---	---	---	---

NA: Not applicable, PDB ID: Identification of the structure in the PDB database.

Glucose transporter 4 (GLUT-4), dipeptidyl peptidase IV (DPP-IV), peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), protein kinase B/AKT (AKT), glucagon-like peptide-1 (GLP-1),  $\alpha$ -amylase, glucose-dependent insulintropic polypeptide (GIP), insulin receptor substrate 1 (IRS1), glycogen synthase kinase 3 (GSK-3), insulin receptor (IR), phosphatidylinositol 3-kinase signaling pathway (PI3K), and insulin-like growth factor (IGF-1).

**Table S4** Characteristics of the *in silico* analyzes of the studies included in the systematic review.

Therapeutic target	Therapeutic agent	<i>In silico</i> technique	Docking score or Binding energy	EPI or RMSD	Most interacting amino acids	Reference
<b>DPP-IV</b> (PDB 2ONC)	Naringin	Molecular docking	Pose 1: -56,89 (considering the complete structure of DPP-IV)  Pose 1: -63,27 (Considering single chain (A chain) outside the DPP-IV homotetramer structure)  Pose 1: -77,95;	---	No information.	Parmar et al. (2012) [39]

			(considering DPP-IV binding pocket(s))			
<b>GLP-1R</b> (PDB 3C5T)	L-Glutamine	Molecular docking	<b>GLP-1R:</b> -6,87	---	<b>GLP-1R:</b> PHE-80, TYR-101, TRP-120, ASP-122, SER-124 and GLU-125	Badole et al. (2013) [40]
<b>PPAR<math>\gamma</math></b> (PDB 2PRG)  <b>Akt</b> (PDB 3O96)  <b>GLUT4</b> (UNIPROT P14672)	Embelin	Molecular docking	<b>PPAR<math>\gamma</math>:</b> - 8,18  <b>Akt:</b> - 5,30  <b>GLUT4:</b> - 6,44	---	<b>PPAR<math>\gamma</math>:</b> LEU- 228, ARG-288 and GLU-295.  <b>Akt:</b> VAL- 271, GLN-79, THR-81, THR-82, and ASP-292  <b>GLUT4:</b> GLN-177, ASN-176, GLN-299.	Gandhi et al. (2013) [41]
<b>DPP-IV</b> (PDB 2ONC)	Glimepiride Sulfonamide (GS)	Molecular docking	<b>DPP-IV:</b> Pose 1: -8,79; Pose 2: -8,41; Pose 3: -8,09; Pose 4: -7,96; Pose 5: -6,60.	---	<b>DPP-IV:</b> ARG-669, PHE-357, LYS-554, TRP-629, TYR-631, TYR-662, TYR-666, GLY-632, GLU-206 and ARG-125.	Parmar et al. (2014) [42]
<b>PPAR<math>\gamma</math></b> (PDB 2PRG)  <b>GLUT4</b> (UNIPROT P14672)	Ficusin	Molecular docking	<b>PPAR<math>\gamma</math>:</b> -7,04  <b>GLUT4:</b> -6,64	---	<b>PPAR<math>\gamma</math>:</b> SER- 289, HIS-323  <b>GLUT4:</b> ASP-427	Irudayaraj et al. (2016) [43]
<b>PPAR<math>\gamma</math></b> (PDB 2PRG)	Isolated compounds of Indian traditional medicinal plants	Molecular docking	<b>3,3- (dimethyl allyl) halfordinol:</b> -8,5  <b>Cucurbitacin B:</b> -8,2  <b>Eremanthin:</b> - 7,87  <b>Nymphayol:</b> - 9,19  <b>Aurapten:</b> -7,6	---	<b>3,3-(dimethyl allyl) halfordinol:</b> ARG-288, TYR-473  <b>Cucurbitacin B:</b> GLU-291, SER-342, THR-268  <b>Eremanthin:</b> SER-342  <b>Nymphayol:</b> ARG-288	Stalin et al. (2016) <sup>a</sup> [45]

					<b>Aurapten:</b> GLN-286, HIS-449	
<b>PPAR<math>\gamma</math></b> (PDB 2PRG)  <b>Akt</b> (PDB 3O96)  <b>GLUT4</b> (UNIPROT P14672)	6-bromoembelin and vilangin	Molecular docking	6-bromoembelin  <b>PPAR<math>\gamma</math>:</b> - 5,60 <b>Akt:</b> -5,48 <b>GLUT4:</b> - 6,74  Vilangin  <b>PPAR<math>\gamma</math>:</b> - 5,98 <b>Akt:</b> - 5,78 <b>GLUT4:</b> - 6,87	---	6-bromoembelin  <b>PPAR<math>\gamma</math>:</b> SER-289, HIS-323 <b>Akt:</b> SER-205, LYS-268 <b>GLUT4:</b> GLY-302, VAL-306, SER-310 Vilangin  <b>PPAR<math>\gamma</math>:</b> GLU-343, SER-342 <b>Akt:</b> ASN-199, TRP-80, LEU-78, SER-216, GLN-59 <b>GLUT4:</b> GLU-136	Stalin et al. (2016) <sup>b</sup> [44]
<b><math>\alpha</math>-amilase</b> (PDB 2QV4)	Taxifolin (TFN)	Molecular docking and molecular dynamics	<b><math>\alpha</math>-amylase:</b> 6,89	Equilibrium was reached quickly after some initial fluctuations, which indicates a stable conformation for a nested structure.	<b><math>\alpha</math>-amylase:</b> TRP-59, TYR-62, GLN-63, ARG-195, GLU-233, HIE-299 and ASP-300	Rehman et al. (2018) [46]
<b>GLP-1</b> (PDB 3IOL)  <b>GIP</b> (PDB 2QKH)	Phytochemicals from PTY-2: tuberostan, puererone, tuberosin, puererin, daidzin,	Molecular docking	<b>GLP-1</b> Tuberostan: 8,15 Puererone: 7,34 Tuberosin: 7,85 Puererin: 6,76 Daidzin: 7,60   <b>Receptor GIP</b> Tuberostan: 7,91 Puererone: 8,31	---	<b>GLP-1:</b> Tuberostan: TYR- 69, LEU-89, TRP-91, LEU-123, CYS-126, GLU-127, GLU-128, TYR-19, GLN-23, LYS-26, ILE-29, ALA-30 e VAL-33.  <b>(Provided only this one for presenting better interaction)</b>  <b>Receptor GIP:</b> Puererone: LYS-16, ILE-	Srivastava et al. (2018) [47]

			Tuberosin: 7,53 Puererin: 7,61 Daidzin: 6,93		17, GLN-19, GLN-20, ASP-21, ASN- 24, GLN-30, PRO-89, TRP- 90, ASN-120 e GLU-122  <b>(Provided only this one for presenting better interaction)</b>	
<b>IR</b> (PDB 1IRK)  <b>GLUT-4</b> (UNIPROT P14672)	$\beta$ -sitosterol	Molecular docking and molecular dynamics	<b>IR:</b> - 10.96  <b>GLUT-4:</b> - 12.25	Balance range from the beginning to the end of the simulation	<b>IR:</b> GLN-107 and GLN-444  <b>GLUT-4:</b> VAL-67, GLN-444, TYR-405, ARG-188, TYR-439 and TRP-173	Ponnulaksh mi et al. (2019) [48]
<b>IRS1</b> (PDB 1IRS)  <b>AKT</b> (PDB 3QKM)	$\beta$ -sitosterol (SIT)	Molecular docking and molecular dynamics	<b>IRS-1:</b> -7,85  <b>AKT:</b> -7,60	Complexes with IRS1 and AKT did not show much fluctuation over the 50ns period.	<b>IRS1:</b> LYS- 161, SER-189 and ALA-259.  <b>AKT:</b> THR- 211 and GLU- 228	Babu et al. (2020) [49]
<b>PPAR<math>\gamma</math></b> (PDB 5TWO)  <b>DPP-IV</b> (PDB 4A5S)	Thymoquinone (2- isopropyl-5- methylbenzo- -1,4 quinone) (TQ)	Molecular docking	<b>PPAR<math>\gamma</math>:</b> -5,7  <b>DPP-IV:</b> -6,3	---	<b>PPAR<math>\gamma</math>:</b> ILE- 262, LYS-263, GLY-284, CYS-285, ARG-288, LEU-330, LEU-333, LEU-340, ILE-341 and SER-342  <b>DPP-IV:</b> TYR-547, SER-630, TYR-631, VAL-656, TRP-659, TYR-662, TYR-666 and VAL-711	Alshahrani (2021) [50]
<b>GLUT 4</b> (PDB 4PYP)	Stevioside	Molecular docking	<b>GLUT 4:</b> -7,8	---	<b>GLUT 4:</b> GLN-113, TYR-168, TRP-173, ARG-188, ALA-190, ARG-336, GLU-359 GLY-404,	Deenadayala n et al. (2021) [51]

					TYR-405 and ARG-433	
<b>GSK3<math>\beta</math></b> (PDB 1Q5K)  <b>PPAR<math>\gamma</math></b> (PDB 1I7I)  <b>DPPIV</b> (PDB 1R9N)  <b>GLUT 4</b> (PDB 5EQG)	Pterostilbene and Andrographolide	Molecular docking	Pterostilbene <b>GSK3<math>\beta</math></b> : -7,51 <b>PPAR<math>\gamma</math></b> : -7,71 <b>DPPIV</b> : -7,0 <b>GLUT 4</b> : -7,13  Andrographolide <b>GSK3<math>\beta</math></b> : - 7,17 <b>PPAR<math>\gamma</math></b> : - 9,33 <b>PPAR<math>\alpha</math></b> : - 5,84 <b>DPPIV</b> : - 6,64 <b>GLUT 4</b> : - 9,36	---	Pterostilbene <b>GSK3<math>\beta</math></b> : VAL-135, LYS-85 <b>PPAR<math>\gamma</math></b> : TYR-473, HIS-449, ARG-288 <b>DPPIV</b> : SER-630, HIS-740, GLU-206 <b>GLUT 4</b> : GLU-396, ASN-431 Andrographolide <b>GSK3<math>\beta</math></b> : VAL-135 and VAL-61 <b>PPAR<math>\gamma</math></b> : TYR-327, ARG-288 and ARG-288 <b>DPPIV</b> : PHE-357, ARG-358, GLU-205, ARG-358 and ARG-358 <b>GLUT 4</b> : GLU-396, ASN-304, GLN-298, ASN-333, GLN-298 and TRP-404	Dound et al. (2021) [52]
<b>DPP-4</b> (PDB 5Y7K)	Phytoconstituents of W. coagulans fruit:  Withanolide D  Sitoindoside IX  Withanone  Withanolide B	Molecular docking	<b>Withanolide D</b> : - 9.2 <b>Sitoindoside IX</b> : -9,8 <b>Withanone</b> : - 7,9 <b>Withanolide B</b> : -9,5 <b>Withaferine A</b> : -8,1	---	<b>Withanolide D</b> : VAL-207 <b>Sitoindoside IX</b> : GLU-205, HIS-740 and TYR-547 <b>Withanone</b> : ARG-125, TYR-662 and VAL-656	Ram et al. (2021) [53]

	<p>Withaferine A</p> <p>Withasomnine</p> <p>Withangulatin A</p> <p>Withacoagulin H</p> <p>Withanolide E</p>		<p><b>Withasomnine:</b> -6,6</p> <p><b>Withangulatin A:</b> -8,8</p> <p><b>Withacoagulin H:</b> -8,9</p> <p><b>Withanolide E:</b> -7,6</p>		<p><b>Withanolide B:</b> TYR-547 and HIS-740</p> <p><b>Withaferine A:</b> SER-209</p> <p><b>Withasomnine:</b> GLU-206</p> <p><b>Withangulatin A:</b> SER-209, ARG-125, GLU-205, GLU-206 and TYR-662</p> <p><b>Withacoagulin H:</b> GLU-206, SER-209, TYR-547, GLU-205 and ASP-663</p> <p><b>Withanolide E:</b> GLU-206, SER-209, ASN-710 and HIS-740</p>	
<b>IGF1, PI3K and AKT</b> (no information on the structure used)	Pentanoic acid, butyric acid and propionic acid	Molecular docking	<p><b>Pentanoic acid with IGF1:</b> around 4.25</p> <p><b>Butyric acid with PI3K:</b> around 4.25</p> <p><b>Propionic acid with AKT:</b> around 4.25</p>	---	<p><b>Pentanoic acid with IGF1:</b> GLY-30 and SER-33</p> <p><b>Butyric acid with PI3K:</b> GLN-846, ARG-849 and CYS-869</p> <p><b>Propionic acid with AKT:</b> LYS-179 and GLU-198</p>	Xia et al. (2021) [54]
<b>DPP-4</b> (PDB 5Y7K)	<p>Withania coagulans fruit phytochemicals:</p> <p>Withacoagin</p> <p>Withasomnine</p> <p>Withanolide E</p>	Molecular docking and molecular dynamics	<p><b>Withacoagin:</b> -9,2</p> <p><b>Withasomnine:</b> -6,6</p> <p><b>Withanolide E:</b> -7,6</p>	Complexes undergo minimal changes during simulations, but the complex with Withasomnine balanced out fastest among all three.	<p><b>Withacoagin:</b> TYR-547</p> <p><b>Withasomnine:</b> GLU-206</p> <p><b>Withanolide E:</b> GLU-206, SER-209, ASN-710 and HIS-740</p>	Kumar et al. (2022) [55]

<b>GLUT 4</b> (PDB 3PCU)	Phytoconstituents of the butanol fraction of <i>B. ferruginea</i> : pyrogallol and sitosterol	Molecular docking	<b>Pyrogallol:</b> -5,0 <b>Sitosterol:</b> -7,9	---	<b>Pyrogallol:</b> ILE-21, ALA-24, ALA-25, GLN-28, LEU-62, PHE-66, ARG-69, LEU-79, ALA-80 and THR-81  <b>Sitosterol:</b> VAL-18, ILE-21, CYS-22, ALA-24, ALA-25, GLN-28, TRP-58, LEU-62, ILE-63, PHE-66, ARG-69, ILE-77, LEU-78, LEU-79, ALA-80, VAL-95, ILE-98, PHE-99, CYS-185, HIS-188, LEU-189 and PHE-192	Oyebode et al. (2022) [56]
<b>AKT1</b> (PDB 2UZS)	Berberine (BBR)+ Paeoniflorin (PF)	Molecular docking	<b>BBR:</b> -7,2 <b>PF:</b> -6,1	---	<b>BBR:</b> GLU-91  <b>PF:</b> LYS-14, LYS-17, ARG-25, ASN-54 and ARG-86	Zhang et al. (2022) [57]
<b>AKT</b> (no information on the structure used)	Beta-Sitosterol as a component of JinXiaoXiao Ke (JXXKD)	Docking molecular	-7,3	---	GLU-91	Lin et al. (2023) [58]

Glucose transporter 4 (GLUT-4), dipeptidyl peptidase IV (DPP-IV), peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), protein kinase B/AKT (AKT), glucagon-like peptide-1 (GLP-1),  $\alpha$ -amylase, glucose-dependent insulintropic polypeptide (GIP), insulin receptor substrate 1 (IRS1), glycogen synthase kinase 3 (GSK-3), insulin receptor (IR), phosphatidylinositol 3-kinase signaling pathway (PI3K), and insulin-like growth factor (IGF-1).

<sup>a</sup> Study 1 by Stalin et al. (2016)

<sup>b</sup> Study 2 by Stalin et al. (2016)

**Table S5** Characteristics of in vivo reassessments of included studies included in the systematic review.

Therapeutic target	In vivo model	Therapeutic agent administered in vivo	In vivo therapeutic target analysis	Results of analysis of in vivo therapeutic targets	Potential Impact for Applicability in Diabetes Treatment	Reference
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<b>DPP-IV</b>	Healthy male albino Wistar rats	Naringin	DPP-IV assay in serum samples	Significantly lower level of serum DPP-IV activity <sup>1</sup>  (Compared to a control group of untreated healthy rats <sup>1</sup> )	Lower glucose level and higher insulin level <sup>1</sup>  (Compared to a control group of untreated healthy rats <sup>1</sup> )	Parmar et al. (2012) [39]
<b>GLP-1R</b>	Male Sprague Dawley Rats with Streptozotocin-Nicotinamide-Induced DM (STZ-NTM)	L-Glutamine	Analysis of GLP-1 active amide concentration in plasma and colon, and during the oral glucose tolerance test  Analysis of GLP-1 mRNA expression from intestinal tissue	Significantly higher level of GLP-1 active amide in plasma and colon and during the oral glucose tolerance test <sup>2</sup>  Increased GLP-1 mRNA expression <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Significantly lower level of glucose, glycated hemoglobin and higher plasma and pancreatic insulin <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Badole et al. (2013) [40]
<b>PPAR<math>\gamma</math></b> <b>Akt</b> <b>GLUT4</b>	Male Wistar rats with streptozotocin-induced DM (STZ) and fed High Fat Diet, cholesterol solution in coconut oil	Embelin	mRNA expression analysis and total proteins of PPAR $\gamma$ , Akt, and GLUT4 from adipose tissue, liver, and skeletal muscle	Increased expression of PPAR $\gamma$ mRNA and total proteins in adipose tissue, liver and skeletal muscle <sup>2</sup>  Increased Akt and GLUT4 mRNA gene expression in adipose tissue <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Improvement in glucose tolerance levels, significant reduction in serum glucose, improvement in plasma insulin level <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Gandhi et al. (2013) [41]
<b>DPP-IV</b>	Wistar albino rats with streptozotocin-induced DM (STZ)	Glimepiride Sulfonamide (GS)	DPP-IV assay in serum samples	Significantly lower level of serum DPP-IV activity <sup>1</sup>  (Compared to the control group of untreated healthy rats <sup>1</sup> )	Significantly lower level of glucose and insulin <sup>1</sup>  (Compared to the control group of untreated healthy rats <sup>1</sup> )	Parmar et al. (2014) [42]

<b>PPAR<math>\gamma</math></b> <b>GLUT4</b>	Male Wistar rats with streptozotocin-induced DM (STZ) fed a high-fat diet	Ficusin	Analysis of PPAR $\gamma$ and GLUT4 mRNA expression in adipose tissue	Increased PPAR $\gamma$ and GLUT4 mRNA expression <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Significantly lower glucose level, better oral glucose tolerance, significantly higher insulin level and glycogen content, considering high doses of the therapeutic agent <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Irudayaraj et al. (2016) [43]
<b>PPAR<math>\gamma</math></b>	Male Wistar albino rats with streptozotocin-induced DM (STZ)	Nymphayol	Analysis of PPAR $\gamma$ mRNA expression from adipose tissue, liver, and skeletal muscle	Significantly higher PPAR $\gamma$ mRNA expression in adipose tissue and slightly increased expression in skeletal muscle. There was no difference in liver <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Improved oral glucose tolerance <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Stalin et al. (2016) <sup>a</sup> [45]

<b>PPAR<math>\gamma</math></b> <b>Akt</b> <b>GLUT4</b>	Male Wistar albino rats with streptozotocin-induced DM (STZ)	6-bromoembelin and vilangin	Analysis of PPAR $\gamma$ , Akt and GLUT4 mRNA and total protein expression in adipose tissue, liver and skeletal muscle	Increased expression of mRNA and total proteins of PPAR $\gamma$ , Akt and GLUT4 in liver and skeletal muscle <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Statistically lower glucose level and improved glucose tolerance <sup>2</sup>  Lower plasma insulin level <sup>1</sup>  (Compared to the control group of untreated healthy rats <sup>1</sup> )  (Compared to control group with untreated diabetes <sup>2</sup> )	Stalin et al. (2016) <sup>b</sup> [44]
<b><math>\alpha</math>-amylase</b>	Albino rats of both sexes with alloxan-induced DM	Taxifolin (TFN)	$\alpha$ -amylase serum level analysis	Statistically lower level of $\alpha$ -amylase when administering high doses of the therapeutic agent <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Statistically lower blood glucose level <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Rehman et al. (2019) [46]
<b>GLP-1</b> <b>GIP</b>	Male Charles Foster rats with streptozotocin-induced DM (STZ)	PTY-2	Plasma analysis of GLP-1 and GIP  Analysis of GLP-1R and GIP-R mRNA expression in pancreatic tissue	Statistically higher levels of GLP-1 and GIP <sup>2</sup>  Increased GLP-1R and GIP-R mRNA expression <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Statistically lower levels of glucose. Greater perimeter and number of islet cells in Langerhans. Significantly higher level of Insulin and Bcl 2 protein expression in the islets of Langerhans <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Srivastava et al. (2018) [47]
<b>IR</b> <b>GLUT-4</b>	Male Wistar albino rats	$\beta$ -sitosterol	Analysis of the expression of adipose tissue IR	Higher levels of IR protein and GLUT-4 <sup>2</sup>	Improved glucose and insulin tolerance, lower	Ponnulaks hmi et al. (2019) [48]

	with DM induced by a high-fat diet and 30% sucrose in drinking water		proteins and GLUT-4 in the cytosol	(Compared to control group with untreated diabetes <sup>2</sup> )	fasting glucose levels <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	
<b>IRS1</b> <b>AKT</b>	Male Wistar albino rats with DM induced by a high-fat diet and 30% sucrose in drinking water	$\beta$ -sitosterol (SIT)	Analysis of mRNA expression and total proteins of IRS-1 and AKT from adipose tissue	Significantly higher expression of mRNA and total proteins of IRS-1 and AKT <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Significant higher expression of mRNA and total proteins of GLUT4, as well as improvement of serine/thionine phosphorylation of Akt <sup>2</sup> .  Improved IR mRNA expression <sub>2,3</sub>  (Compared to control group with untreated diabetes <sup>2</sup> )  (Compared to DM group treated with standard drug <sup>3</sup> )	Babu et al. (2020) [49]
<b>PPAR<math>\gamma</math></b> <b>DPP-IV</b>	Male Wistar rats with streptozotocin-induced DM (STZ) fed a high-fat diet	Thymoquinone (2-isopropyl-5-methylbenzo-1,4 quinone) (TQ)	Nuclear protein analysis (adipose tissue) to measure PPAR $\gamma$ and DPP-IV serum analysis	Higher expression of PPAR $\gamma$ in adipose tissue and lower of DPP-IV <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Significantly lower level of glucose, insulin and HOMA-IR, improvement in OGTT <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Alshahrani (2021) [50]
<b>GLUT 4</b>	Male Wistar rats with DM induced by a high-fat diet and 30% sucrose in drinking water	Stevioside	Muscle GLUT 4 mRNA expression analysis	Increased GLUT 4 mRNA expression <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Reduction of elevated fasting glucose levels and improved glucose tolerance <sup>3</sup>  Restoration of insulin levels <sup>1</sup>  Increased IR gene expression in muscles <sup>2</sup>  (Compared to a control group of untreated healthy rats <sup>1</sup> )	Deenadaya lan et al. (2021) [51]

					(Compared to control group with untreated diabetes <sup>2</sup> )  (Compared to DM group treated with standard drug <sup>3</sup> ).	
<b>GSK3<math>\beta</math></b> <b>PPAR<math>\gamma</math></b> <b>DPPIV</b> <b>GLUT 4</b>	Male Wistar albino rats with streptozotocin-induced DM (STZ)	A blend of Ptyrone <sup>TM</sup> , containing combination of hydroalcoholic extract of Andrographis paniculata Nees. and Pterocarpus marsupium Roxb.	Analysis of GSK3 $\beta$ , PPAR $\gamma$ and GLUT 4 mRNA expression in liver tissue and DPP-IV assay in plasma samples	Increased expression of PPAR $\gamma$ , GSK3 $\beta$ and GLUT4. No significant inhibition of DPP4 <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Lower fasting blood glucose level <sup>2</sup> .  (Compared to control group with untreated diabetes <sup>2</sup> )	Dound et al. (2021) [52]
<b>DPP-4</b>	Wistar rats with dexamethasone-induced DM fed a sucrose-rich diet along with carbohydrate-rich foods	Ethanol extracts of W. coagulans fruit	DPP-IV assay in serum samples	Statistically low levels of DPP-4 <sup>1,2</sup>  (Compared to a control group of untreated healthy rats <sup>1</sup> )  (Compared to control group with untreated diabetes <sup>2</sup> )	Statistically low levels of glucose, insulin, insulin resistance. Statistically increased levels of $\beta$ -cell function and insulin sensitivity <sup>1,2</sup>  Statistically increased levels in islet cell mass in pancreatic tissues and restoration of vascular tissues <sup>2</sup>  (Compared to a control group of untreated healthy rats <sup>1</sup> )  (Compared to control group with untreated diabetes <sup>2</sup> )	Ram et al. (2021) [53]
<b>IGF1, PI3K and AKT</b>	Male C57BL/6J mice with DM induced by a high-fat diet followed by	CS polysaccharides (CSP)	Analysis of IGF1, PI3K, and AKT mRNA expression.  Immunohistochemical analysis of IGF1 and AKT expression in the colon	Increased expression of IGF1, PI3K, and AKT mRNA <sup>2</sup>  Significantly higher expression of IGF1 and	Lower fasting glucose levels, and rapid decrease in glucose spikes during the OGTT test <sup>2</sup> .  Serum insulin levels close to	Xia et al. (2021) [54]

	streptozotocin (STZ)			AKT in the colon <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	those of untreated healthy control animals <sup>1</sup> .  (Compared to a control group of untreated healthy rats <sup>1</sup> )  (Compared to control group with untreated diabetes <sup>2</sup> )	
<b>DPP-4</b>	Male Wistar albino rats with streptozotocin-induced DM (STZ)	Extract of Withania coagulans	DPP-IV assay in serum samples	Statistically low levels of DPP-4 <sup>1,2</sup>  (Compared to a control group of untreated healthy rats <sup>1</sup> )  (Compared to control group with untreated diabetes <sup>2</sup> )	Statistically low level of glucose, insulin and HOMA indexes <sup>1,2</sup>  Regeneration and restoration of the islets of Langerhans <sup>2</sup>  (Compared to a control group of untreated healthy rats <sup>1</sup> )  (Compared to control group with untreated diabetes <sup>2</sup> )	Kumar et al. (2022) [55]
<b>GLUT 4</b>	Male Sprague Dawley rats with DM induced by fructose (10%) followed by streptozotocin (STZ)	Bridelia ferruginea extract	Analysis of GLUT 4 mRNA molecular expression in liver and muscle	Increased GLUT 4 mRNA expression <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Higher levels of liver glycogen when administering high doses of the therapeutic agent <sup>3</sup>  (Compared to DM group treated with standard drug <sup>3</sup> )	Oyebode et al. (2022) [56]
<b>AKT1</b>	Male C57BL/6J mice with high-fat diet-induced DM	Berberine (BBR)+ Paeoniflorin (PF)	Western blot analysis with primary AKT1 monoclonal antibodies in liver tissues	Higher levels of AKT1 phosphorylation <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Lower fasting glucose levels, lower OGTT glucose spikes <sup>2</sup>  (Compared to control group with untreated diabetes <sup>2</sup> )	Zhang et al. (2022) [57]
<b>AKT</b>	Male Goto-Kakizaki (GK) rats with DM induced by a high-	JinXiaoXiaoK e Decoction (JXXKD)	AKT mRNA analysis	Statistically low levels of AKT expression <sup>4</sup>	Lower Fasting Glucose Levels and HOMA-IR <sup>4</sup>  (Compared to the untreated model group <sup>4</sup> )	Lin et al. (2023) [58]

	sugar, high-fat diet			(Compared to the untreated model group <sup>4</sup> )		
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<sup>1</sup> These data are related to the test group compared to the untreated healthy control group.

<sup>2</sup> These data are related to the test group compared to the control group with untreated diabetes.

<sup>3</sup> These data are related to the test group compared to the control group with diabetes treated with the standard drug.

<sup>4</sup> These data are related to the test group compared to the group fed a high-sugar and high-fat diet during the experiment.

Glucose transporter 4 (GLUT-4), dipeptidyl peptidase IV (DPP-IV), peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), protein kinase B/AKT (AKT), glucagon-like peptide-1 (GLP-1),  $\alpha$ -amylase, glucose-dependent insulintropic polypeptide (GIP), insulin receptor substrate 1 (IRS1), glycogen synthase kinase 3 (GSK-3), insulin receptor (IR), phosphatidylinositol 3-kinase signaling pathway (PI3K), and insulin-like growth factor (IGF-1).

<sup>a</sup> Study 1 by Stalin et al. (2016).

<sup>b</sup> Study 2 by Stalin et al. (2016).