RESEARCH PAPER

Exploring the Antidiabetic Potential of *Putranjiva roxburghii* through Computational Approaches

Mahvish Jamal[0009-0001-1666-0244]* and Mhaveer Singh[0000-0001-9951-5685]

School of Pharmaceutical Sciences, IFTM University, Moradabad-244102

Address for correspondence:Mahvish Jamal (✉) School of Pharmaceutical Sciences, IFTM University, Moradabad-244102 (E-mail: mahvishjamaal@gmail.com)

Abstract

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycaemia and is associated with severe microvascular, macrovascular, and neuropathic complications. The increasing global prevalence of type 2 diabetes and the limitations of existing synthetic antidiabetic drugs, including adverse effects and high treatment costs, have intensified the search for safer and more effective plant-derived therapeutic agents. *Putranjiva roxburghii*, a medicinal plant widely used in traditional Ayurvedic and Unani systems of medicine, contains diverse phytoconstituents with potential pharmacological activities. The present study aimed to evaluate the antidiabetic potential of phytochemicals from *Putranjiva roxburghii* through molecular docking studies against α-glucosidase (PDB ID: 6C9X), a key therapeutic target involved in postprandial glucose regulation. Thirty phytoconstituents reported from the leaves of the plant were selected and docked using Auto Dock Vina. The docking interactions were analysed by comparing binding energies and interaction profiles with the co-crystallized inhibitor voglibose. The results demonstrated that Amentoflavone and 4"'-O-methylamentoflavone exhibited the highest binding affinities with docking scores of –9.2 kcal/mol and showed multiple crucial interactions with key active-site residues, including ARG404, ASP197, TRP169, and ASP420. Chlorogenic acid, Gallocatechin, and Caffeic acid also displayed favourable binding profiles with significant interactions corresponding to those observed in the native ligand complex. Among the active-site residues, ASP420 emerged as the most critical amino acid for ligand binding, while the conserved water molecule HOH1350 played an important role in stabilizing ligand–protein interactions. The findings suggest that Amentoflavone, 4"'-O-methylamentoflavone, Chlorogenic acid, Gallocatechin, and Caffeic acid may serve as promising α-glucosidase inhibitors and potential lead compounds for the development of novel antidiabetic agents. This study highlights the utility of *in silico* approaches in identifying bioactive phytoconstituents and provides a scientific basis for further *in vitro* and *in vivo* investigations of *Putranjiva roxburghii* as a potential source of antidiabetic therapeutics.

Keywords: *Putranjiva roxburghii*, Diabetes mellitus, α-Glucosidase, Molecular docking, Phytoconstituents.

How to cite this article: Jamal M, Singh M. Exploring the Antidiabetic Potential of Putranjiva roxburghii through Computational Approaches. Int J Drug Deliv Technol. 2026;16 (56s): 422-437. DOI: 10.25258/ijddt.16.56s.47

Source of support: Nil.

Conflict of interest: None.

1 Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by abnormally high blood glucose levels. (1–3) Type 1 diabetes (idiopathic and fulminant), type 2 diabetes, gestational diabetes, hybrid forms, slowly emerging immune-mediated diabetes, ketosis-prone type 2 diabetes, and other unique varieties are among the several categories of diabetes. Hyperglycaemia is the hallmark of type 2 diabetes mellitus, which is caused by a combination of insufficient insulin secretion, excessive or incorrect glucagon secretion, and resistance to insulin action. Numerous microvascular, macrovascular, and neuropathic problems are linked to poorly managed type 2 diabetes. (2) One of the deadliest illnesses is diabetes. According to the most recent data from the NCD Risk Factor Collaboration (2022), there were 828 million people worldwide, and more than 95% of them had type 2 diabetes, making it a disease of civilization. (4-5) A metabolic condition known as chronic hyperglycaemia is brought on by either insufficient insulin secretion, compromised insulin action, or both. Notably, insulin is a key anabolic hormone that influences how proteins, fats, and carbs are metabolized. According to estimates from the International Diabetes Federation, 1 in 11 persons worldwide between the ages of 20 and 79 had diabetes in 2015. By 2040, experts predict that the number of people with DM will rise from 415 to 642 million, with the largest increase occurring in populations moving from low to middle-income levels.(6–8) An estimated 828 million persons (those 18 years of age and older) had diabetes in 2022 (95% credible interval [CrI] 757–908), up 630 million (554–713) from 1990. With a posterior probability of greater than 0·80, the age-standardized prevalence of diabetes rose in 155 nations for men and 131 countries for women between 1990 and 2022.Low-income and middle-income nations in Southeast Asia (like Malaysia), South Asia (like Pakistan), the

Middle East and North Africa (like Egypt), and Latin America and the Caribbean (like Jamaica, Trinidad and Tobago, and Costa Rica) had the biggest rises. (9) It is estimated that there will be 69.9 million cases of diabetes in India by 2025, the great majority of which would remain undiagnosed. (10) According to WHO forecasts, by 2030, diabetes would rank as the seventh leading cause of death. (11)

Table1. Medications, their mechanism of action and side effects. (12-13)

Class	Example Drugs	Mechanism (concise)	Key Adverse Effects
Biguanides	Metformin	Reduces hepatic gluconeogenesis and improves peripheral insulin sensitivity.	Gastrointestinal upset (nausea, diarrhea), vitamin B12 deficiency with long-term use; rare lactic acidosis in renal/hepatic impairment.
Sulfonylureas	Glibenclamide, Glipizide, Glimepiride	Stimulate pancreatic β-cell insulin release via ATP-sensitive K^+ channel closure.	Hypoglycaemia, weight gain, cutaneous reactions; mixed evidence for cardiovascular risk.
Meglitinides	Repaglinide, Nateglinide	Short-acting insulin secretagogues primarily targeting post-prandial glucose excursions.	Hypoglycaemia (typically less frequent than with sulfonylureas), mild weight gain.
Thiazolidinediones (TZDs)	Pioglitazone, Rosiglitazone	PPAR-γ agonists that enhance insulin sensitivity in adipose tissue and muscle.	Fluid retention/edema, weight gain, risk of heart failure exacerbation, increased fracture risk; pioglitazone has been linked to bladder cancer in some studies.
Alpha-glucosidase inhibitors	Acarbose, Miglitol	Delay intestinal carbohydrate digestion to blunt post-meal glycemic rise.	Flatulence, abdominal discomfort, diarrhea.
DPP-4 inhibitors	Sitagliptin, Saxagliptin, Vildagliptin	Inhibit incretin degradation, thereby enhancing glucose-dependent insulin secretion and lowering glucagon.	Nasopharyngitis/URTI, headache; rare pancreatitis and severe arthralgia.
SGLT-2 inhibitors	Empagliflozin, Canagliflozin, Dapagliflozin	Block renal glucose reabsorption leading to glucosuria and reduced plasma glucose.	Genital mycotic infections, urinary tract infections, volume depletion/hypotension, rare euglycemic diabetic ketoacidosis.
GLP-1 receptor agonists (injectable)	Exenatide, Liraglutide, Semaglutide	Mimic GLP-1 to promote glucose-dependent insulin secretion, suppress glucagon, delay gastric emptying, and enhance satiety.	Nausea, vomiting, diarrhea; rare pancreatitis; possible thyroid C-cell tumor signal in animal studies.
Amylin analogues	Pramlintide	Slows gastric emptying, suppresses post-prand	Nausea, hypoglycemia when combined with insulin.

		ial glucagon, increases satiety; adjunct to insulin.	
Insulin therapy	Rapid-acting (Lispro, Aspart), Short-acting (Regular), Intermediate (NPH), Long-acting (Glargine, Detemir)	Replaces or supplements endogenous insulin to control fasting and post-prandial glucose.	Hypoglycemia, weight gain, lipohypertrophy or lipoatrophy at injection sites; allergic reactions are rare.

Many of those synthetic medications are either directly or indirectly produced from plants, which are always regarded as one of the most dependable sources of disease-curing compounds. According to recent research, plants and plant-based products may have promising antidiabetic effects. Since ancient times, plant sources of antidiabetic compounds have been widely used since they are comparatively safer and far less expensive than synthetic pharmaceuticals. They are also mentioned in many traditional treatments, such as those used in Chinese, Korean, and Indian cultures. (14–15)

Numerous *in vitro* and *in vivo* studies have shown the antidiabetic potential of a wide variety of medicinal plants. However, the precise biochemical pathways and particular phytoconstituents that provide glucose-modulating actions are not entirely understood for many botanicals. Molecular docking, computational pharmacology, and dynamic simulations are examples of *in silico* approaches that provide crucial tools for understanding these mechanisms in this context. These methods assist identify the most promising bioactive compounds against important antidiabetic targets and insulin receptor components by identifying plausible molecular targets, modelling ligand–protein interactions, and rating compound potency using binding affinity assessments.

Additionally, *in silico* research offers a number of important benefits, such as the ability to quickly and affordably do high-throughput virtual screening of large phytochemical libraries. It makes it easier to generate hypotheses regarding atomic-level mechanisms of action, which can direct experimental validation. It streamlines efforts in phytochemical separation and extract standardization by directing the discovery of lead compounds. It lessens the need for early-stage clinical research and animal testing, which helps to allay ethical worries and save resources. It facilitates the rational design and optimization of natural analogues by supporting the creation of SAR (structure–activity relationships). It supports the investigation of polypharmacological interactions, which is consistent with the multi-target action of herbal remedies in the treatment of complex diseases such as diabetes. When combined, computational techniques serve as a potent supplement to laboratory research, hastening the identification and verification of plant-derived antidiabetic medications and enabling the logical conversion of conventional cures into cutting-edge, evidence-based therapies. Compared to the conventional time-consuming method (from choosing the plant to separating chemicals in accordance with the bioassay guidelines), the CADD methodology is quicker and more effective. (16)

For thousands of years, people have utilized various sections of *Putranjiva roxburghii*, a member of the Putranijvaceae family, as a traditional herbal cure in Ayurvedic and Unani medicine. (17) Southeast Asia, the Indian Subcontinent, Japan, southern China, and New Guinea are the natural habitats of this plant. It is extensively farmed throughout Asia, especially in Bangladesh, India, Nepal, Thailand, Indochina, Myanmar, and Sri Lanka. (18) It is referred to as "Putranjiv" in Bangladesh, "child life tree" in English, Jivanputra, Putranjiva, Kumarajiva, Mava, Pavitra, and Putrajiva, and Karupali or Irukolli in India's Siddha medical system. "Pootranjeeva" is composed of the words "pootra" (son) and "jeeva" (life). *Putranjiva roxburghii* is also known by the names Kudrajuvi, Patravanti, Jivputrak, and Nageia. According to reports, it works well for liver problems, fever, and infertility (19). *Putranjiva roxburghii* has anthelmintic, anticancer, anti-inflammatory, antioxidant, aphrodisiac, diuretic, and laxative properties (20, 21, 22, 23, and 24). (25) Burning sensations, filarial, inflammatory, and ocular conditions are treated with leaves and seed paste. (26) Numerous chemical components from the families of tannins, saponins, steroids, alkaloids, and flavonoids are present in putanjiva. (27–28) Palmitic acid, hexadecanoic acid, 9-octadecanoic acid, linoleic acid ethyl ester, ethyl oleate, octadecanoic acid, bis(2-ethylhexyl) phthalate, N-propyl heptyl ether, 5-ethyl hydantoin, octadec-9-enoic acid, 1,2-benzene dicarboxylic acid, and isopropyl isothiocyanate are all present in the plant's seeds. (29-30) Friedlein, Methylputranjate, Putrone, Putranjivadione,

Roxburghonic acid, and Roxburghonol are all found in the plant's bark. (31) Putranoside-D, Putranoside-A, Putranoside-A methyl ester, 4-O-α-rhamnopyranoside, 3'-O-methylellagic acid. (32) The plant's leaves include Putralone, a new 10α-hydroxy-25 nor D: Afriedo-olean-9(11)-en-3 one, 3β-acetoxy-cycloart-24-en-23-one, Adian-5-en-3β,29-diol, 3β-acetoxy-adian-5-ene, Roxburghonic acids, Friedelin, Friedlan-3α-ol, Oleanic acid, and Erthrodiol. (33–34) Cyclohexanol, 5-methyl-2-(1-methylethenyl), 6-Octen-1-ol, Geraniol, and (1R,2S,5R)-2-(2-Hydroxy-2-propanyl)-5-methylcyclohexanol are found in the plant's fruit peel. (35-36)

Alpha glucosidase (6c9x) is a crucial target among the several targets for type 2 diabetes. (37) Alpha-glucosidase inhibitors prevent the small intestine from absorbing carbohydrates. Enzymes that transform complicated nonabsorbable carbohydrates into simple absorbable carbohydrates are competitively inhibited by them. Glucoamylase, sucrase, maltase, and isomaltase are some of these enzymes. They lower the increase in postprandial blood glucose concentrations by roughly 3 mmol/L by postponing the absorption of carbohydrates. (38) These inhibitors work well for those who are more susceptible to hypoglycaemia or lactic acidosis, which makes them good substitutes for people who shouldn't use traditional antidiabetic drugs like metformin and sulfonylureas. (39) In order to develop a physiologic functional diet or lead molecule for the treatment of diabetes, numerous efforts have been conducted in recent years to find effective α-glucosidase inhibitors from natural sources. Numerous phytoconstituent α-glucosidase inhibitors, such as alkaloids, flavonoids, anthocyanins, terpenoids, phenolic compounds, glycosides, and others, have been found in plants. (40) These lower HbA1c (glycated haemoglobin) levels by 0.5–1.0%. There are no signs of hypoglycaemia, and they are specific for postprandial hyperglycaemia. (41) Alpha-glucosidase inhibitors usually do not cause hypoglycaemia, or low blood sugar, which is a common adverse effect of certain other diabetic treatments since they do not stimulate insulin secretion. Alpha-glucosidase inhibitors are often weight-neutral, in contrast to some drugs that may result in weight increase. In fact, the way these drugs impact the absorption of carbohydrates may cause some people to lose a little weight. (42)

In order to potentially shed light on the underlying molecular mechanisms required for enzyme inhibition, the goal of this study was to investigate a wide range of bioactive substances (phytoconstituents) from *Putranjiva roxburghii* leaves and to examine how these substances interacted with target proteins.

2 Materials and methods

2.1 Dataset

For the docking investigations, 30 bioactive phytoconstituents were selected from the literature (Table 2) namely 1. 3β-Acetoxyadiane-5-ene 2. 3β-Acetoxy-Cycloart-24-en-23-one 3. 3-O-methyl ellagic acid-4-O-α-rhamnopyranoside 4. Adian-5-ene-3β,29-diol 5. Amentoflavone 6. β-Amyrin 7. Caffeic Acid 8. Catechin 9. Chlorogenic Acid 10. Epicatechin 11. Erythrodiol 12. Ferulic Acid 13. Friedlein 14. Gallocatechin 15. Genistic Acid 16. Laminitol 17. 4"'-O-methylamentoflavone 18. Methyl Putranjivate 19. Oleanolic Acid 20. Putraflavone 21. Putrajivadion 22. Putralone 23. Putranjivic Acid 24. Putrol 25. Putrone 26. Roxburghonic Acid 27. Syringic Acid 28. Syringin Methyl Ether 29. Umbelliferone 30. Vanillic Acid.

2.2 Preparation of ligands

The ligands or molecules from the dataset were drawn using ChemDraw. Chem3D was used to import the similar two-dimensional structures and convert them into three dimensions. As part of further preparation, the structures were reduced using the default parameters. The structures were imported into the Autodock 4.2 program to detect torsions after being saved in the mol format. In order to facilitate further docking study, the structures were ultimately saved in the pdbqt format.

2.3 Preparation of protein

For the docking studies, the target protein with pdb ids of 6C9X was acquired from the protein data bank. Alpha-glucosidase in interaction with voglibose is represented by the 6C9X protein, a member of the hydrolase class, with a resolution of 1.46 Å. Autodock 4.2 was used to minimize the downloaded target protein. The co-crystallized ligands in each protein indicate that the polar hydrogens were supplied after the superfluous water molecules were eliminated. The Kollmann charges were added concurrently with the missing residues. For additional docking research, the produced proteins were stored in the pdbqt format.

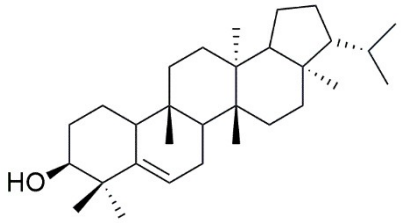
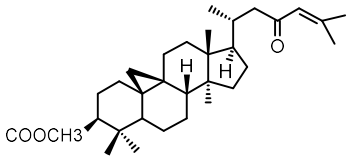
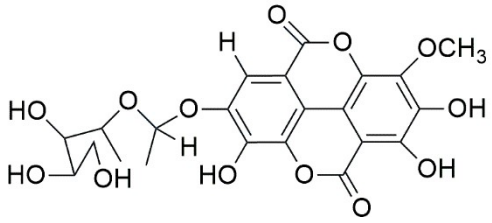
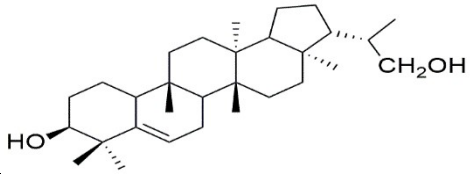
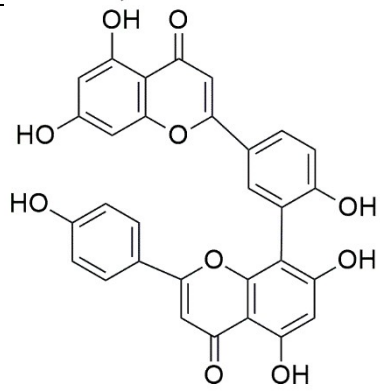
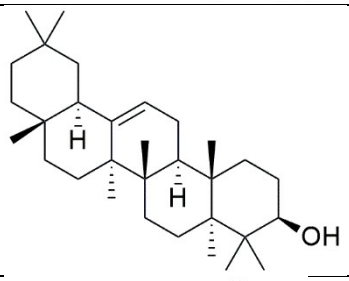
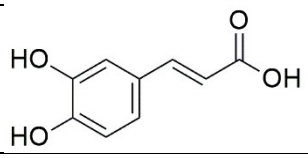
2.4 Preparation of the grid box

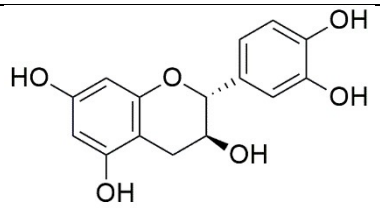
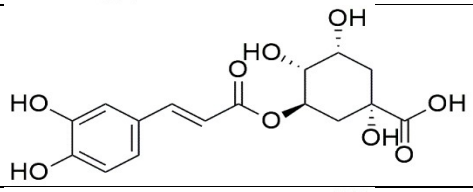
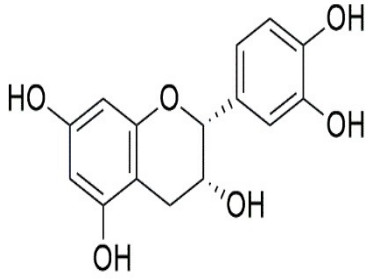
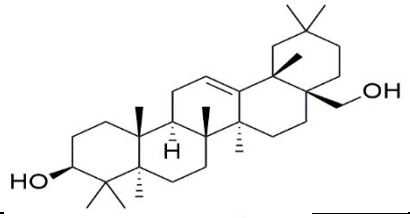
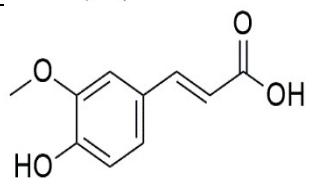
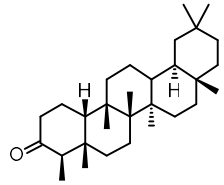
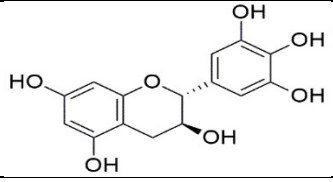
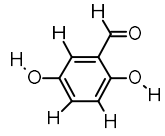
The docking grid box is the exact area of the protein structure where the ligands bind. This is primarily identified by the co-crystallized ligand. The XYZ coordinates of the co-crystallized ligands of the downloaded targets were used to define the grid box. The coordinates of the proteins 6C9X were 8.190, -6.470, and -10.450.

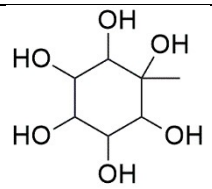
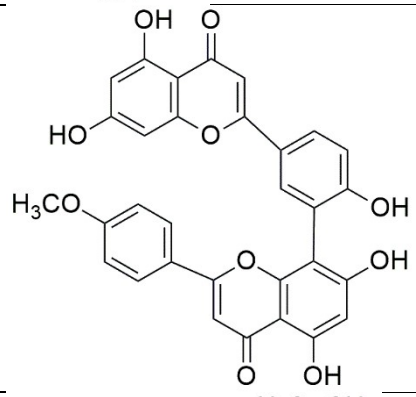
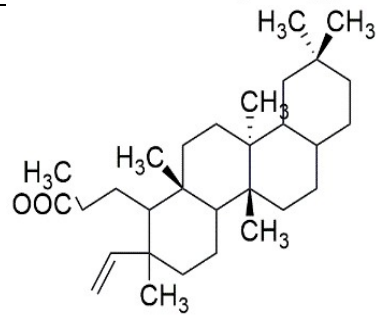
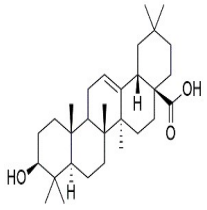
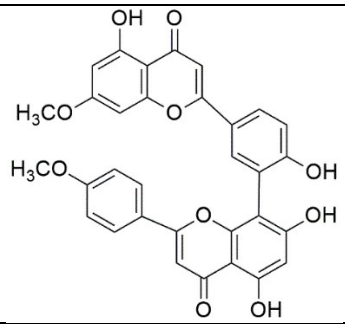
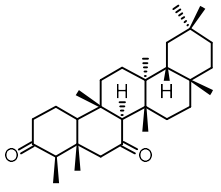
2.5 Docking studies

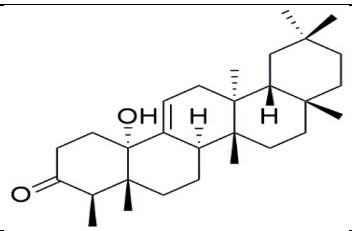
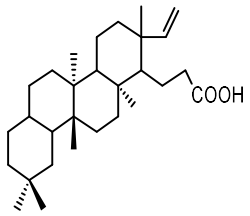
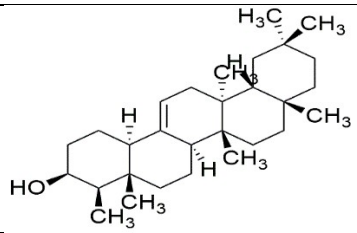
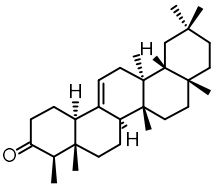
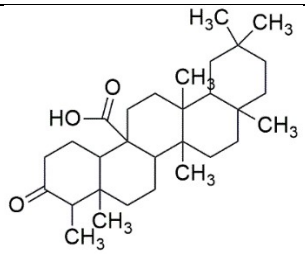
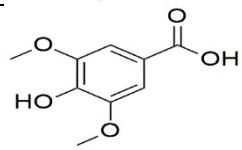
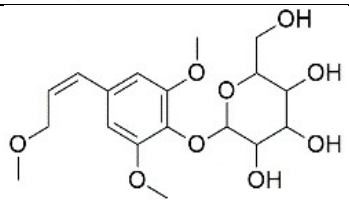
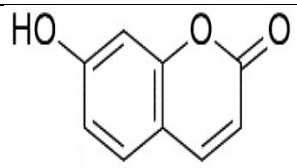
The ligands were docked using Autodock Vina. This software creates configuration files that primarily include the protein and ligands in pdbqt formats along with the grid box's XYZ coordinates.

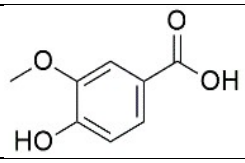
Table 2- Compound and their Structure

S.No.	Compounds	Structure
1.	3β-Acetoxyadiane-5-ene	
2.	3β-Acetoxy-Cycloart-24-en-23-one	
3.	3-O-methyl ellagic acid -4-O-α-rhamnopyranoside	
4.	Adian-5-ene-3β,29-diol	
5.	Amentoflavone	
6.	β-Amyrin	
7.	Caffeic Acid	

8.	Catechin	
9.	Chlorogenic Acid	
10.	Epicatechin	
11.	Erythrodiol	
12.	Ferulic Acid	
13.	Friedlein	
14.	Gallocatechin	
15.	Genistic Acid	

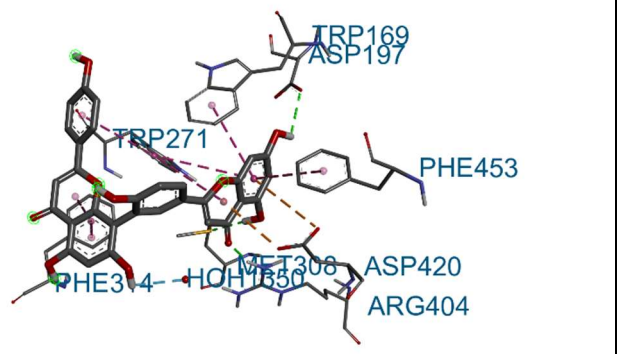
16.	Laminitol	
17.	4”’-O-methylamentoflavone	
18.	Methyl Putranjivate	
19.	Oleanolic Acid	
20.	Putraflavone	
21.	Putrajivadion	

22.	Putralone	
23.	Putranjivic Acid	
24.	Putrol	
25.	Putrone	
26.	Roxburghonic Acid	
27.	Syringic Acid	
28.	Syringin Methyl Ether	
29.	Umbelliferone	

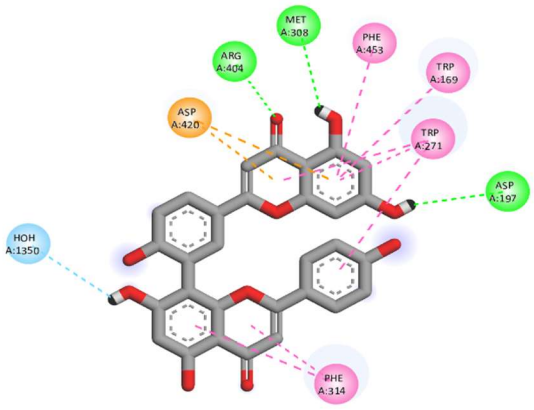
30.	Vanillic Acid	

RESULTS AND DISCUSSION

The careful analysis of the original co-crystal (Voglibose) in the protein 6C9X reveals interactions with HIS478, ASP197, ASP420, ARG404, ASP73, and TRP169 amino acids apart from the three water molecules namely, HOH843, HOH852, and HOH1350. The presence of these interactions are crucial for activity. In order to identify the most important phytoconstituents the docking results were analyzed both in terms of docking score and poses. The study of the most stable pose reveals the interacting amino acid residues which may be compared with the interactions present in the original co-crystal. The results revealed that the most important amino acid was ASP420 with 13 interactions followed by TRP169 (11 interactions), HIS478 and Arg404 (6 interactions each), ASP197 (5 interactions), and ASP73 (1 interactions). The HOH1350 water molecule showed the most interactions (15) followed by HOH843 and HOH852 with 5 and 4 interactions respectively. Among the phytoconstituents used in the docking studies, Amentoflavone, Laminitol, Caffeic acid, and Syringic acid showed 5 interactions common to the original co-crystal, while, Gallocatechin, 4"'-O-methylamentoflavone, and chlorogenic acid displayed 4 common interactions. The best docking score of -9.2 belonged to amentoflavone and meth 4"'-O-methylamentoflavone. Although some phytoconstituents such as Putraflavone, Putrajivadion, and Friedlein etc. displayed good docking scores of -8.9 to -8.6 but did not show good number of interactions common to the co-crystal, for example, Putrajivadion, and Friedlein did not show any common interaction while, Putraflavone showed only 2 common interactions which indicate that the interacting amino acid residues were not fruitful for activity. Among the docked compounds, the compounds which showed 4-5 common interactions were further studied in depth. Amentoflavone and 4"'-O-methylamentoflavone displayed 5 and 4 common interactions respectively with an excellent docking score of -9.2. The 3D and 2D docked poses of the most important phytoconstituents are given in Figure 1.



(a)



(b)

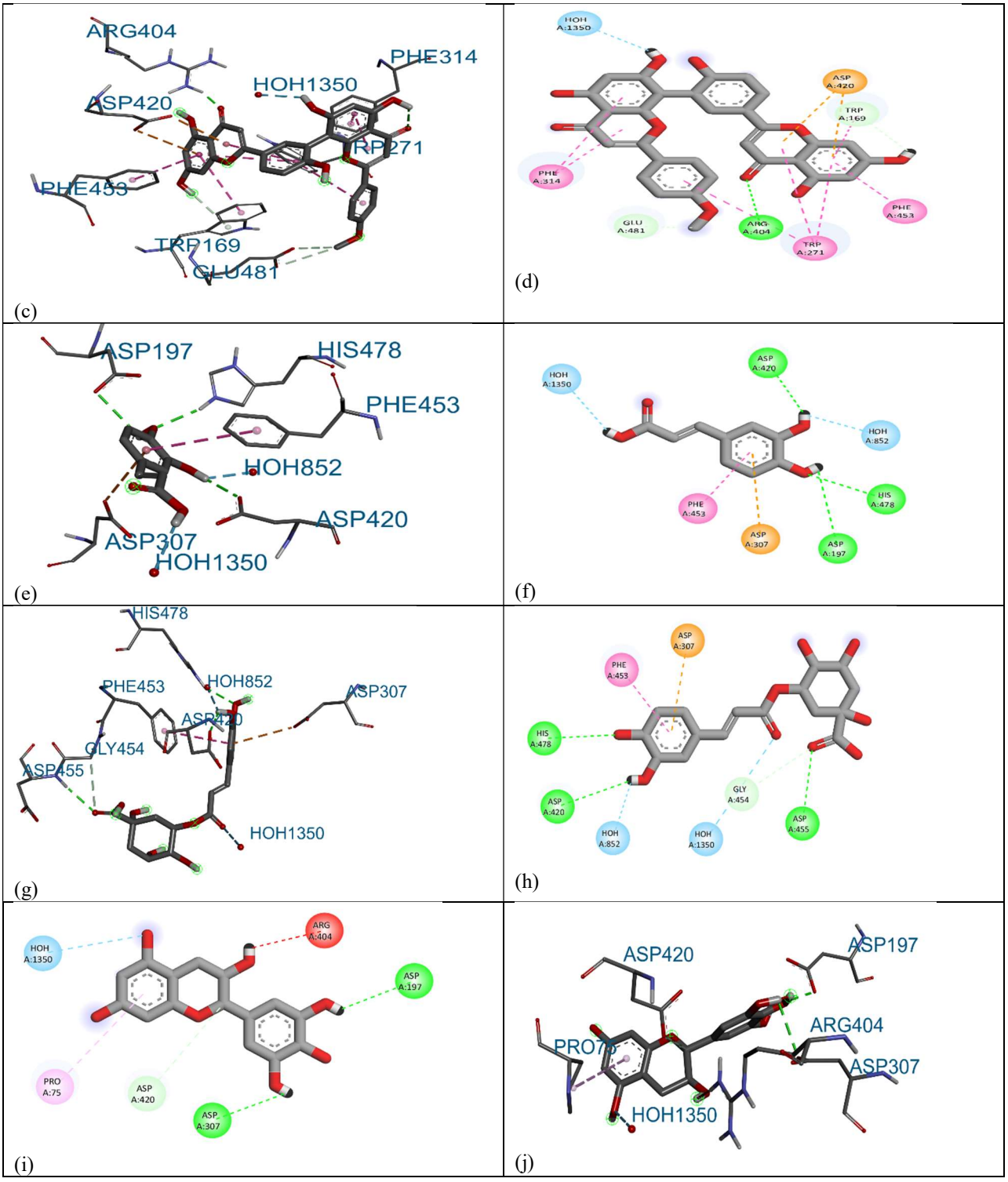


Figure 1. The 3D and 2D docked poses of the important phytoconstituents. (a) 3D pose of Amentoflavone (b) 2D pose of Amentoflavone (c) 3D pose of 4"'-O-methylamentoflavone (d) 2D pose of 4"'-O-methylamentoflavone (e) 3D pose of Caffeic acid (f) 2D pose of Caffeic acid (g) 3D pose of Chlorogenic acid (h) 2D pose of Chlorogenic acid (i) 3D pose of Gallocatechin (j) 2D pose Gallocatechin

The interacting residues found in these compounds were, ARG404, ASP197, TRP169, ASP420, HOH1350 in amentoflavone and ARG404, TRP169, ASP420, HOH1350 in 4"'-O-methylamentoflavone.

The next best compound according to the docking score was chlorogenic acid which had a docking score of -7.9 and displayed 4 interactions with HIS478, ASP420, HOH852, HOH1350 followed by Gallocatechin with a docking score of -7.6 and displaying 4 interactions with ARG404, ASP420, ASP197 and HOH1350. Caffeic acid and Laminitol showed a lower docking scores (-7.0 and -6.9 respectively) as compared to above compounds but interacted with a maximum of 5 common interactions, viz. ASP197, HIS478, ASP420, HOH852, HOH1350 (Caffeic acid) and ASP197, ASP420, TRP169, HOH843, HOH852 (Laminitol). Among the compounds displaying the maximum of 5 interactions, Syringic acid showed the minimum docking score of -4.9. Among the above studied compounds which displayed 4 to 5 common interactions, the interacting amino acid ARG420 was found in 6 phytoconstituents followed by the presence of HOH1350 also in 6 phytoconstituents. The absence of ARG420 in the syringic acid and simultaneously its presence in phytoconstituents displaying good docking scores, viz. Amentoflavone, Caffeic acid, Chlorogenic acid, Gallocatechin, Laminitol, and 4"'-O-methylamentoflavone indicates a crucial role played by the amino acid residue. Hence, the overall analysis of the docking results reveals that the most important phytoconstituents for activity as antidiabetic activity are Amentoflavone and 4"'-O-methylamentoflavone, Chlorogenic acid, Gallocatechin and Caffeic acid with ASP420 amino acid being the most important amino acid residue responsible for binding. The results also indicate a positive role of the water molecule HOH1350 in the crucial binding of the phytoconstituents in the active site for displaying antidiabetic activity.

Table 3: Binding energy (kcal/mol) of bio-molecules in *Putranjiva roxburghii* to Alpha Glucosidase (6c9x)- X=8.190, Y=-6.470, Z=-10.450

S.No.	Compound	Energy	Interactions	Bond
1	3β-Acetoxyadiane-5-ene	-8.1	PHE314	Pi- Sigma bond, Hydrophobic bond
			ASP455	Hydrogen bond
2	3β-Acetoxy-Cycloart-24-en-23-one	-8.2	VAL351	Pi- Alkyl, Hydrophobic bond
			MET347	Pi- Alkyl, Hydrophobic bond
			LYS422	Hydrogen bond
			PRO75	Carbon –Hydrogen bond
			ASN421	Carbon –Hydrogen bond
			GLY454	Carbon –Hydrogen bond
3	3-O-methyl ellagic acid -4-O-α-rhamnopyranoside	-7.9	GLY454	Carbon –Hydrogen bond
			GLU481	Carbon –Hydrogen bond
			ASP455	Hydrogen bond
			LYS422	Hydrogen bond
			ASP420	Hydrogen bond
			ASP307	Hydrogen bond
			PRO75	Pi- Alkyl, Hydrophobic bond
			HOH843	Hydrogen bond
			HOH1350	Hydrogen bond
4	Adian-5-ene-3β,29-diol	-7.8	LYS422	Hydrogen bond
			PRO75	Hydrogen bond
			PHE314	Pi- Sigma bond, Hydrophobic bond
5	Amentoflavone	-9.2	MET308	Hydrogen bond
			ARG404	Hydrogen bond
			ASP197	Hydrogen bond
			PHE453	Pi-Pi T-Shaped Hydrophobic bond
			TRP169	Pi-Pi T-Shaped Hydrophobic bond
			TRP271	Pi-Pi T-Shaped Hydrophobic bond
			PHE314	Pi-Pi T-Shaped Hydrophobic bond

			ASP420	Pi-Anion Electrostatic bond
			HOH1350	Hydrogen bond
6	β-Amyrin	-7.6	PRO75	Pi- Alkyl, Hydrophobic bond
			PHE453	Pi- Alkyl, Hydrophobic bond
			TRP169	Pi- Alkyl, Hydrophobic bond
			TRP271	Pi- Alkyl, Hydrophobic bond
			TRP305	Pi- Alkyl, Hydrophobic bond
			TRP417	Pi- Alkyl, Hydrophobic bond
			HIS478	Pi- Alkyl, Hydrophobic bond
			LYS422	Hydrogen bond
7	Caffeic Acid	-7.0	HOH1350	Hydrogen bond
			HOH852	Hydrogen bond
			ASP420	Hydrogen bond
			HIS478	Hydrogen bond
			ASP197	Hydrogen bond
			PHE453	Pi-Pi T-Shaped Hydrophobic bond
			ASP307	Pi-Anion Electrostatic bond
8	Catechin	-7.3	HOH1350	Hydrogen bond
			PRO75	Pi- Alkyl, Hydrophobic bond
			ASP420	Carbon –Hydrogen bond
			ASP197	Hydrogen bond
9	Chlorogenic Acid	-7.9	ASP307	Pi-Anion Electrostatic bond
			PHE453	Pi-Pi Stacked Hydrophobic bond
			HIS478	Hydrogen bond
			ASP420	Hydrogen bond
			ASP455	Hydrogen bond
			HOH852	Hydrogen bond
			HOH1350	Hydrogen bond
			GLY454	Carbon –Hydrogen bond
10	Epicatechin	-6.8	ASP73	Hydrogen bond
			GLU481	Hydrogen bond
			TRP169	Pi-Pi T-Shaped Hydrophobic bond
			ALA480	Pi- Alkyl, Hydrophobic bond
			PRO75	Pi- Alkyl, Hydrophobic bond
			HOH1350	Hydrogen bond
11	Erythrodiol	-7.4	HOH1350	Hydrogen bond
12	Ferulic Acid	-6.7	ASP307	Carbon –Hydrogen bond
			ASP420	Carbon –Hydrogen bond
			HOH1350	Hydrogen bond
			HIS478	Unfavourable Donor-Donor bond
			TRP417	Pi- Alkyl, Hydrophobic bond
13	Friedlein	-8.5	PHE314	Pi- Sigma bond, Hydrophobic bond
14	Gallocatechin	-7.6	HOH1350	Hydrogen bond
			PRO75	Pi- Alkyl, Hydrophobic bond
			ASP420	Carbon –Hydrogen bond
			ARG404	Unfavourable Donor-Donor bond
			ASP197	Hydrogen bond
			ASP307	Hydrogen bond
15	Genistic Acid	-6.5	ASP420	Hydrogen bond
			ARG404	Hydrogen bond
			ASP307	Pi-Anion Electrostatic bond
16	Laminitol	-6.9	TRP271	Hydrogen bond
			ASP197	Hydrogen bond

			ASP420	Hydrogen bond
			ASP307	Hydrogen bond
			MET308	Hydrogen bond
			HOH843	Hydrogen bond
			HOH852	Hydrogen bond
			TRP169	Carbon –Hydrogen bond
17	4”’-O-methylamentoflavone	-9.2	HOH1350	Hydrogen bond
			PHE314	Pi-Pi Stacked Hydrophobic bond
			PHE453	Pi-Pi Stacked Hydrophobic bond
			TRP271	Pi-Pi Stacked Hydrophobic bond
			TRP169	Carbon –Hydrogen bond
			GLU481	Carbon –Hydrogen bond
			ARG404	Hydrogen bond
			ASP420	Pi-Anion Electrostatic bond
18	Methyl Putranjivate	-8.0	PRO75	Pi- Alkyl, Hydrophobic bond
			PHE314	Pi- Alkyl, Hydrophobic bond
			TRP169	Pi- Sigma bond, Hydrophobic bond
19	Oleanolic Acid	-7.4	HOH1350	Hydrogen bond
20	Putraflavone	-8.9	GLU481	Hydrogen bond
			TRP271	Hydrogen bond
			PRO75	Pi- Alkyl, Hydrophobic bond
			PHE453	Pi- Alkyl, Hydrophobic bond
			VAL351	Pi- Alkyl, Hydrophobic bond
			HOH1350	Hydrogen bond
			PHE314	Pi-Pi Stacked Hydrophobic bond
			TRP169	Pi-Pi Stacked Hydrophobic bond
21	Putrajivadion	-8.6	PHE314	Pi- Sigma bond, Hydrophobic bond
22	Putralone	-8.3	ASP455	Hydrogen bond
			LYS422	Hydrogen bond
			GLY454	Carbon –Hydrogen bond
			PHE314	Pi- Sigma bond, Hydrophobic bond
23	Putranjivic Acid	-7.5	PHE453	Pi- Alkyl, Hydrophobic bond
			PRO75	Pi- Alkyl, Hydrophobic bond
			PHE314	Pi- Alkyl, Hydrophobic bond
			ASP420	Unfavourable Acceptor- Acceptor bond
24	Putrol	-8.3	TRP169	Pi- Alkyl, Hydrophobic bond
			TRP271	Pi- Alkyl, Hydrophobic bond
			ASP420	Unfavourable Acceptor- Acceptor bond
			HOH1350	Hydrogen bond
			PHE314	Pi- Sigma bond, Hydrophobic bond
25	Putrone	-8.4	LYS422	Hydrogen bond
			ASP455	Hydrogen bond
			GLY454	Carbon –Hydrogen bond
26	Roxburghonic Acid	-7.9		
27	Syringic Acid	-4.9	HIS478	Unfavourable Donor-Donor bond
			ARG404	Unfavourable Donor-Donor bond
			ASP307	Carbon –Hydrogen bond
			HOH1350	Hydrogen bond
			HOH843	Hydrogen bond
			PHE453	Pi-Pi Stacked Hydrophobic bond

			TRP271	Alkyl, Hydrophobic bond
			TRP169	Alkyl, Hydrophobic bond
			TRP417	Alkyl, Hydrophobic bond
			ILE198	Alkyl, Hydrophobic bond
28	Syringin Methyl Ether	-6.2	LYS422	Hydrogen bond
			ASP455	Hydrogen bond
			ASP420	Hydrogen bond
			ASP404	Hydrogen bond
			GLY481	Hydrogen bond
			PRO75	Carbon –Hydrogen bond
29	Umbelliferone	-6.9	ARG404	Hydrogen bond
			PHE453	Pi-Pi T-Shaped Hydrophobic bond
			HOH852	Hydrogen bond
			TRP169	Pi- Sigma bond, Hydrophobic bond
			ASP307	Pi-Anion Electrostatic bond
30	Vanillic Acid	-5.8	TRP169	Pi- Sigma bond, Hydrophobic bond
			ILE198	Pi- Alkyl, Hydrophobic bond
			HIS478	Unfavourable Donor-Donor bond
			ASP307	Pi-Anion Electrostatic bond
			TRP271	Pi- Alkyl, Hydrophobic bond

CONCLUSION

The present study highlights the significance of key amino acid residues and water molecules in governing the binding interactions of phytoconstituents within the active site. ASP420 emerged as the most critical residue, with consistent involvement across high-performing compounds, while HOH1350 demonstrated a supportive role in stabilizing ligand binding. Among the screened phytoconstituents, Amentoflavone and 4"'-O-methylamentoflavone exhibited superior docking scores and interaction profiles, followed by Chlorogenic acid, Gallocatechin, and Caffeic acid. These findings suggest important role of docking results in terms of docking scores and pose and may help in screening of phytoconstituents and in designing and development of new compounds as potential antidiabetic agents.

REFERENCES

1. Sapra A, Bhandari P. Diabetes. StatPearls. 2023 Jun 21. PubMed PMID: 31855345.
2. Lu X, Xie Q, Pan X, Zhang R, Zhang X, Peng G, Zhang Y, Shen S, Tong N.Type 2 diabetes mellitus in adults: pathogenesis, prevention and therapy. Signal Transduction and Targeted Therapy 2024 9:1. 2024 Oct 2;9(1):1–25.
3. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H, Martín C.Pathophysiology of Type 2 Diabetes Mellitus. Int J Mol Sci. 2020 Sep 1;21(17):6275.
4. Młynarska E, Czarnik W, Dzieża N, Jędraszak W, Majchrowicz G, Prusinowski F, Stabrawa M, Rysz J, Franczyk B.Type 2 Diabetes Mellitus: New Pathogenetic Mechanisms, Treatment and the Most Important Complications. International Journal of Molecular Sciences 2025, Jan 27;26(3):1094.
5. Liu J, Wang Y, Zhang L, Dang S. Global trends and inequalities in diabetes prevalence and treatment coverage among adults aged ≥ 45 years, 1990-2040: Insights from the NCD-RisC database. Diabetes Metab Res Rev. 2026;42(4):e70164.
6. Antar SA, Ashour NA, Sharaky M, Khattab M, Ashour NA, Zaid RT, Roh EJ, Elkamhawy A, Al-Karmalawy AA. Diabetes mellitus: Classification, mediators, and complications; A gate to identify potential targets for the development of new effective treatments. Biomed Pharmacother. 2023 Dec;168:115734.
7. Tiwari P. Recent Trends in Therapeutic Approaches for Diabetes Management: A Comprehensive Update. J Diabetes Res. 2015;2015:340838.
8. Iheagwam FN, Iheagwam OT. Diabetes mellitus: The pathophysiology as a canvas for management elucidation and strategies. Med Nov Technol Devices. 2025 Mar 1;25:100351.

9. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: A pooled analysis of 1108 population-representative studies with 141 million participants. Lancet. 2024;404(10467):2077-2093.
10. Mathur P, Leburu S, Kulothungan V. Prevalence, Awareness, Treatment and Control of Diabetes in India From the Countrywide National NCD Monitoring Survey. Front Public Health. 2022 Mar 14;10:748157.
11. Alam S, Hasan MK, Neaz S, Hussain N, Hossain MF, Rahman T. Diabetes Mellitus: Insights from Epidemiology, Biochemistry, Risk Factors, Diagnosis, Complications and Comprehensive Management. Diabetology 2021 Apr 16;2(2):36–50.
12. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022 Nov 1;45(11):2753-2786.
13. Kahn SE, Cooper ME, Prato S Del. Review Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future The epidemic of type 2 diabetes. www.thelancet.com. 2014;383.
14. Alam S, Sarker MMR, Sultana TN, Chowdhury MNR, Rashid MA, Chaity NI, Zhao C, Xiao J, Hafez EE, Khan SA, Mohamed IN. Antidiabetic Phytochemicals From Medicinal Plants: Prospective Candidates for New Drug Discovery and Development. Front Endocrinol (Lausanne). 2022 Feb 24;13:800714.
15. Li GQ, Kam A, Wong KH, Zhou X, Omar EA, Alqahtani A, Li KM, Razmovski-Naumovski V, Chan K. Herbal medicines for the management of diabetes. Adv Exp Med Biol. 2012;771:396-413.
16. Xu X. New concepts and approaches for drug discovery based on traditional Chinese medicine. Drug Discov Today Technol. 2006 Sep 1;3(3):247–53.
17. Pandey R, Fulara BT. The therapeutic uses of *Putranjiva roxburghii*: Review Article. International Journal of Veterinary Sciences and Animal Husbandry. 2022 Jul 1;7(4):51–4.
18. Britto JS. Pharmacognostic Studies of *Putranjiva roxburghii* Wall. (Putranjivaeceae). International Journal of Pharmacognosy and Phytochemical Research. 2017;9(7):1035–44.
19. Supriy B, Vijayakumar K, Subramanian N. Mahendradas, D. K. Medicinal values of *Putranjiva roxburghii*-A review. International Journal of Current Pharmaceutical Research, 2017, 9, 5-8.
20. Oraon S, Mondal S. Studies on Allelopathic Effect of Aqueous Leaf Extract of *Putranjiva Roxburghii* Wall. on Seed Germination and Early Growth of Chickpea (Cicer Arietinum L.). Indian J Agric Res. 2020 Apr 1;54(2):193–8.
21. Afzal M, Hafeez A, Asif DM, Asif M. A Review on Botanical Description, Phytoconstituents, And Biological Activity of *Drypetes Roxburghii.* Educational Administration: Theory and Practice. 2024 Apr 25;30(4):6240–7.
22. Balkrishna A, Sharma VK, Das SK, Mishra N, Bisht L, Joshi A, Sharma N. Characterization and Anti-Cancerous Effect of *Putranjiva roxburghii* Seed Extract Mediated Silver Nanoparticles on Human Colon (HCT-116), Pancreatic (PANC-1) and Breast (MDA-MB 231) Cancer Cell Lines: A Comparative Study. Int J Nanomedicine. 2020;15:573.
23. Mangmool S, Duangrat R, Rujirayunyong T, Anantachoke N. Anti-inflammatory effects of the Thai herbal remedy Yataprasen and biflavonoids isolated from *Putranjiva roxburghii* in RAW264.7 macrophages. J Ethnopharmacol. 2024 Jun 12;327.
24. Chinmaya A, Sudharshan SJ, Valleesha NC, Kekuda TRP, Rajeshwara AN, Murthuza S. In vitro antioxidant activity of *Putranjiva roxburghii* Wall seed by DPPH radical scavenging activity. Global Journal of Pharmacology 2009, 3 (1): 53-58.
25. Dar P, Faisal M, Dar A, Waqas U. Journey Describing Biological Activities and Chemical Constituents in the Leaves, Stem Bark and Seed of *Putranjiva roxburghii*. Current Traditional Medicine. 2018 Dec 1;4(4):263–78.
26. Sudharshan SJ, Chinmaya A, Valleesha NC, Prashith Kekuda TR, Rajeshwara AN, Syed Murthuza. Central Nervous System Depressant and Analgesic Activity of Methanolic Extract of Drypetes roxburghii Wall in Experimental Animal Model. Research J. Pharm. and Tech.2 (4): Oct.-Dec. 2009; Page 854-857.

27. Rama Murthy KS, Reddy MC, Kiran AR, Emmanuel S. Ethnobotany and Chemistry of Drypetes roxburghii - A Review J. Trop. Med. Plants. 2013 Jan-Dec 14, 109-114.
28. Wansi JD, Wandji J, Sewald N, Nahar L, Martin C, Sarker SD. Phytochemistry and pharmacology of the genus Drypetes: A review. J Ethnopharmacol. 2016 Aug 22;190:328–53.
29. Kala C, Khan NA. Isolation and characterization of isopropyl isothiocyanate isolated from seeds of *Drypetes roxburghii* wall and its anti-platelet and anti-thrombotic activity. Sci Afr. 2020 Nov 1;10:e00658.
30. Emasushan M, John Britto SSeed Oil Extraction and Phytochemical Analysis of *Putranjiva roxburghii* Wall. (Putranjivaceae). Vol. 5. 2018 [cited 2026 Jun 1];5.
31. Shanker K, Mishra S, Bawankule D. Assessment of chemical composition and antidiabetic potential of Putranjiva roxburghii twigs. In: Proceedings of 5th International Electronic Conference on Medicinal Chemistry. Basel, Switzerland: MDPI; 2019.
32. Kumar A, Chowdhury SR, Chakrabarti T, Majumdar HK, Jha T, Mukhopadhyay S. A new ellagic acid glycoside and DNA topoisomerase IB inhibitory activity of saponins from *Putranjiva roxburghii*. Nat Prod Commun. 2014 May 1;9(5):675–7.
33 Mukherjee T, Sarkar T, Paul P, Chakraborty AK, Jaisankar P, Mukhopadhyay SB. Putralone, a novel 10alpha-hydroxy-25-nor D:A friedo-oleanane triterpenoid from *Putranjiva roxburghii*. Nat Prod Commun. 2012;7(4):511–3.
34. Bijekar S. Antimicrobial Activity of Isolated Flavonoid Fractions from *Drypetes Roxburghii* (Wall.) Huresawa and Its Phytochemical Fingerprinting. International Journal of Innovative Research in Science, Engineering and Technology 2015 July, 4, I (7), 6214- 6224.
35. Hasan MM, Al Mahmud MR, Islam MG. GC-MS Analysis of Bio-active Compounds in Ethanol Extract of *Putranjiva roxburghii* Wall. Fruit Peel. Pharmacognosy Journal. 2019;11(1):146–9.
36. Naik A, Pandya P, Mankad A. A comprehensive review on phytochemicals and medicinal properties of *Putranjiva roxburghii* wall. International Association of Biologicals and Computational Digest. 2023 May 15;2(1):234–40.
37. Tan K, Tesar C, Jedrzejczak R, Joachimiak A. The crystal structure of the alpha-glucosidase (gh 31) from *Ruminococcus obeum* ATCC 29174 in complex with voglibose. Worldwide Protein Data Bank. 2018 Mar 7.
38. Akmal M, Patel P, Wadhwa R. Alpha Glucosidase Inhibitors. StatPearls. 2024 Feb 28. PubMed PMID: 32496728.
39. Van de Laar FA, Lucassen PLBJ, Akkermans RP, Van de Lisdonk EH, Rutten GEHM, Van Weel C. Alpha-glucosidase inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2005 Apr 20;2005(2):CD003639.
40. Kashtoh H, Baek K-H. Recent updates on phytoconstituent alpha-glucosidase inhibitors: An approach towards the treatment of type two diabetes. Plants. 2022;11(20):2722.
41. Mohajan D, Mohajan HK. Alpha-Glucosidase Inhibitors (AGIs): A New Class of Oral Medication for Treatment of Type 2 Diabetes Patients. Journal of Innovations in Medical Research. 2024 Dec;3(4):1–6.
42. Van de Laar FA. Alpha-glucosidase inhibitors in the early treatment of type 2 diabetes. Vasc Health Risk Management. 2008;4(6):1189–95.