# A systematic Review on Terpenes As Potential Antidiabetic Compounds



**Maruti Shelar[1], Roshani Paradhi[2]**

[1]Department of Pharmacognosy, Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune 411018, (MS) India.

[2]Department of Pharmaceutical Quality Assurance, Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune 411018. (MS) India.

**Corresponding author-**

Dr. Maruti K. Shelar

Associate Professor, Department of Pharmacognosy ,

Dr. D.Y. Patil Institute of Pharmaceutical Sciences & Research.

Email- marutikshelar7@gmail.com

## ABSTRACT:

Type -II diabetes is a major outbreak and fastest growing disease in this modern lifestyle society. A current treatment includes various oral hypoglycemics, insulin and balance diet rules. There is need of remedy to develop a plant-based drug for Type- II diabetes management. The present review introduces terpenes a plant secondary metabolite having significant antidiabetic activity. The study focused mainly on various pathways of terpenes acting as antidiabetic isolated from plants and tested in-vivo, in-vitro and Insilico. The Literature on terpenes showed antidiabetic activity were selected. This review summarizes the terpenes classification, various target of type- II diabetes, pathways of terpenes phytoconstituents for treatment of diabetes, Insilico studies on in-vivo targets and other clinical significance of terpenes responsible for producing a therapeutic effect in the management of diabetes.These secondary metabolites are have structural diversity which has significant curative potential against diabetes by lowering blood glucose level and inhibiting α-amylase, α- glucosidase enzymes and aldose reductase enzyme, and also suppresses other diabetic complications by antihyperlipidemic activity, antioxidant activity have been beneficial for management of Type -II diabetes. By the study terpenes are futuristic medicament and alternative in the management of Diabetes *mellitus.*

**KEYWORDS:** Type-II Diabetes, Terpenes, pathways, in-vivo, in-vitro and Insilico.

**DOI Number: 10.14704/nq.2022.20.13.NQ88172** **Neuro Quantology 2022; 20(13):1376-1391**

## INTRODUCTION

The world full of diabetes suffering population, according to recent papers worldwide 415 million peoples live with diabetes [1]. a future prospective show increase in cases may reach to 592 million by 2035. Diabetes Mellitus characterise by an increase in blood sugar level because of insulin dysfunction [2]. Major distress found in Type 2 diabetes.90% of patients with type II diabetes having microvascular and macrovascular complications which may affect both patients and their carers by psychologically and physically (1).So many of the phytoconstituents having a promising activity to cure diabetes. Traditional medicinal plants are non-toxic, effective and they show less or no side effect. They contain mainly alkaloids, terpenoids, carotenoids and flavonoids as ant-diabetic [3]. Diabetes has two types of complications. Type 1 diabetes caused due to autoimmune-mediated destruction of β-cells,

however, the people with type 2 diabetes having insulin resistance or impairment in insulin secretion. In the group of antidiabetics drugs usually encounter the carbohydrate digestion and minimizing the uptake of blood glucose level such as α-glucosidase inhibitors; reducing the release or production of glucose by the liver (e.g., biguanides). Other groups such as thiazolidinediones relatively increase the sensitivity of insulin secretory target organs and rest of others drugs are insulin secret analogies meglitinide, sulfonylureas, DPP-4 inhibitors and glucagon-like peptide 1(GLP-1) [4]. usually, these drugs become less efficacious after using for a long period of time and might get side effects like gastrointestinal complications due to too many expenses and long duration of treatment may cause patient inconvenience so, they much need for testing novel drugs for more efficacy with promising safety and affordable to patients (4).Terpenoids are generally important secondary metabolites produce from medicinal plants. They are diverse in a structure that is derived from mevalonic acid having an isoprene unit. To date about more than 50 thousand terpenoids is isolated from plants [5]. The word terpene itself shows the presence of hydrocarbons with olefinic bonds [6]. The use of terpenoids is different according to their characteristics some terpenoids are important for the growth and development of plants, some of them maintains the defence system and many other volatile terpenoids used as raw spices. In 1960 limited terpenoids was discovered by a human, in 1970 researchers founds effectiveness of artemisinin against malaria. In the late 1990s, the separation, purification and chemical analysis of terpenoids was got more focused [7]. Isoprene (2-methylebuta-1,3-diene) is a basic unit of terpenoids. They are classified by rearranging isoprene units in the linear arrangement based on the number of carbon atoms and their structural organization. According to isoprene rule all the terpenoids having top to the bottom linkage of isoprene units. Some of the terpenoids having common top-bottom linkage (e.g., Triterpenoids, carotenoids) .While other compounds having top-middle linkage of isoprene unit (i.e., irregular monoterpenoids[8]. There are two main synthetic pathways for terpenoids, one is the MVA pathway active in the cytoplasm and other is 1-deoxy-D-xylulose-5-phosphate (DXP) pathway in plastids. Mevalonate pathway produces triterpenes, sesquiterpenes and sterol as a secondary metabolite. However, the DXP pathway produces mono-, di- and tetraterpenes as a secondary metabolite [9].



## PROPERTIES

Terpenes are a large group of natural products that are found primarily in higher plants are designed as secondary metabolites, Terpenes have been found in bacteria, fungi, algae, plants rich in essential oils, resins, waxes, and rubber latex), and some animals (especially insects, and marine organisms, with a wide range of building and construction[10]. Terpenes are formed by the monomer isoprene ($C_5H_8$) people who connect with the head-to-tail to form a linear chain, or which are arranged in rings. The connections are divided into hemiterpenes (1 unit of isoprene; C5), monoterpenes (2-units of the isoprene; C10), sesquiterpenes (3 units of isoprene; C15), (4 units of isoprene; C20), sesquiterpenes (5 units of isoprene; C25), triterpenes (6 units of isoprene; C30), tetraterpenes (8 units of isoprene; C40) and polyterpenes (8 units of the isoprene), on the basis of isoprene units [11]. Terpenes are, be it in the form of hydrocarbons, whether in the form of oxygen-containing compounds, known as terpenes. Terpene and its derivatives are useful in the treatment of various diseases, and show anti-cancer, anti-oxidant, anti-inflammatory, and anti-viral properties. Plant shows an herbal effect, as a rule, is rich in terpenes. In this review, examine, it was isolated from a medicinal plant, and is associated with antidiabetic effects. The main objective of the study was to gather information on the diet of the terpenes used in the treatment of diabetes mellitus, as well as to establish the relationship between structure and activity. It is also having a clear understanding of the pharmacologic profile, the brief of the topics, and in the future, the Saint-Petersburg, russia, which will give impetus to further research an issue and its derivatives, as in a futuristic antidiabetic agent[12].

## TOXICITY OF TERPENES

If a large size molecules entry of terpene through the cell membrane is a tough task. By

means of a number of experiments, and their transmission to the cells through the blood-brain barrier and accumulation in the liver, this can be poisonous, and is available to the public. Chronic consumption of natural terpene-rich foods can increase their bioavailability, leading to accumulation in the blood and tissues [13].

**VARIOUS TARGETS FOR TYPE II DIABETES**:

Type II diabetes is a chronic metabolic disorder followed by hypertension and hyperlipidaemia. The antidiabetics are used objectively for insulin secretion, inhibit the α glucosidase, insulin sensitizers. There are some metabolic and cellular targets are theoretically incorporated and can take in consideration to improve the pancreatic function by anti-inflammatory and antioxidation, modulate the response of insulin secretory tissue and make a better way to reduce complications[14].

The various approaches are available for diabetes treatment such as[15]

1. Insulin mimetics
2. Enhancement of insulin resistance
3. Hepatic glucose inhibitors
4. Agents inhibit glucose uptake
5. Insulin sensitizers (3)

Other than this some novel targets are come across for type 2 diabetes Peroxisome proliferator-activated receptor gamma (PPAR-γ), Glucagon-like peptide receptor agonists (GLP-1 agonist), Dipeptidyl peptidase-4 (DPP-4) and Protein tyrosine phosphatase 1B (PTP1B) inhibitors.

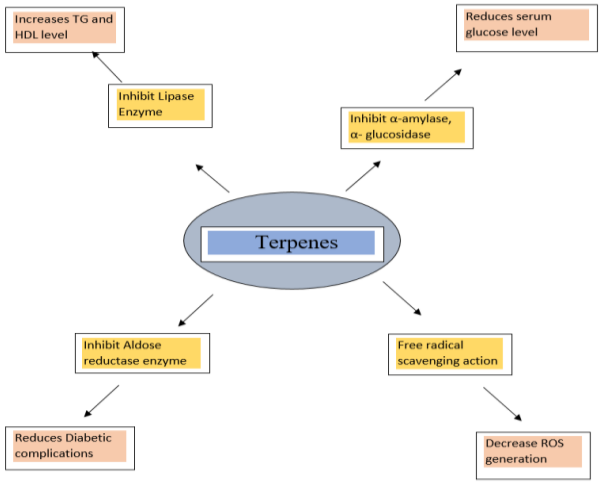



**Fig 1 .The various pathway of terpenes to treat Type -II diabetes mellites.**

TG: Triglyceride, HDL: High-Density Lipoprotein, ROS: Reactive oxygen species

1. **α-amylase and α- glucosidase inhibition activity of terpenes**: [16]

The enzymes **α** - amylase and **α** -glucosidase plays a vital role in the digestion of starch and produces glucose, the inhibition of such enzymes becomes a major pathway to cure diabetes. Currently, acarbose and miglitol like drugs are used as hypoglycemic agents and help to reduce post-prandial blood glucose level. A bioactive compound *Momordica charantia L.* has been used for diabetes management and used as a nutrient. 1-7 compounds are isolated from bitter melon (*Momordica charantia L.*) has significant inhibitory action against **α** -amylase but less than acarbose standard. Among the 7 compounds momordicoside G has higher **α** -amylase inhibitory activity, while gentisic acid 5-O-β- **α** -xyloside has low inhibition activity; when compounds tested for **α** -glucosidase activity at 0.67 and 1.33 mM gentisic acid 5-O-β- **α** -xyloside has maximum inhibitory action and Momordicoside I has low inhibition at 1.33mM. The compound momordicoside G, karaviloside XI like cucurbitane triterpenes shows the same potent inhibitory activity against both enzymes (14). Selected terpenes from essential oil were evaluated for antidiabetic activity with **α** -amylase; citral, eucalyptol, β-pinene, myrcene, eugenol and terpineol these are terpenes compounds are investigated for having **α** -amylase activity. The enzyme assay performs with **α** -amylase as it hydrolyses 2-chloro-4-nitrophenyl- **α** -D-maltotrioside (CNPG3) into 2-chloro-4-nitrophenyl- **α** -D-maltosides (CNPG2), 2-chloro-4- nitrophenol (CPNP) and maltotriose, glucose. The concentration of produced 2-chloro-4- nitrophenol (CPNP) estimates the amylase activity and the absorbance is measured at 440nm. The conclusion stated that much lesser concentration of β-pinene and concentration of eugenol is most effective terpene concentrations for **α** -amylase inhibition activity; the appropriate mixing concentrations of terpenes enhances **α** -amylase activity (15). The oil from the leaf of *Eucalyptus camaldulensis Dehn*. (Myrtaceae) having chemical composition of 99.10% of essential oil with p-cymene (68.43%), 1,8-cineole (14%),1-(S)- **α** -pinene (3.45%) and R-(+)-limonene (2.84%). The

eucalyptus oil shows 55.00± 2.00% inhibition activity for **α** -amylase. The 50% inhibition of **α** -amylase at a low concentration of eucalyptus oil was indicated, while at 93.25±2.64% the highest inhibition of **α** -glucosidase by eucalyptus oil was recorded (16). The extract of *Juniperus phoenicea* plant results in essential oil with identified 37 compounds. The 96.98% essential oil contains high percentages of terpenes compounds; **α** -Pinene, limonene, D-3-Carene, Germacrene B, Germacrene D and **α** -cadinene to check antidiabetic activity invitro **α** -amylase inhibition assay by CNPG3 method was performed. The various extracts of *J. phoenicea* (ethanol, methanol, hexane and essential oil) are used for assay except ethanolic extract other showed a potent inhibitory action against **α** -amylase. The IC50 value of **α** -amylase assay are followed as essential oil > hexane extract > methanol extract (17). A novel abietane diterpene and triterpenoids were isolated from *Salvia Africana-lutea.* 19-acetoxy-12-methoxycarnosic acid, 3β-acetoxy-7- **α** -methoxyrosmanol, 19-acetoxy-7α-methoxyrosmanol, 19-acetoxy-12-methoxy carnosol, clinopodiolides A and B are abietane diterpenes and some triterpenoids namely oleanolic, and ursolic acids, 11,12-dehydroursolic acid lactone and β-amyrin. These compounds are subjected to in vitro **α** -amylase and **α** -glucosidase activity. the ursolic acid shows strong **α** -glucosidase activity and Oleanolic acid show greater **α** -amylase inhibition activity. The study concluded with a statement that terpenoids present in the plant of Salvia *Africana-lutea* have **α** -amylase and **α** -glucosidase activity and antioxidant property which mainly responsible in the chronic disease management such as diabetes[17].

2. **Antihyperlipidemic activity of terpenes:** [17]

Hyperglycemic conditions in type 2 diabetes enhances the major risk of increased body weight by alteration in lipid metabolism it mainly due to increased synthesis and release of very-low-density lipoprotein and low clearance rate by the lipase enzyme this will cause atherosclerosis condition in adults. Mycelia from antrodia camphorate which is a parasitic microorganism present in the inner wall of *Cinnamomum kanehirai* Hay. A cultured mycelium contains sesquiterpenes, triterpenoids, steroids, phenyl derivatives, fatty acids and lignans. Triterpenoid dehydroeburicoic acid was reported for antidiabetic and antihyperlipidemic activity using the in-vitro study of GLUT4 and phosphor-Akt (Ser 473)/ Total Akt proteins and also in vivo study with STZ-induced mice model. Dehydroeburicoic acids lower up to 42- 46.5% of blood glucose level at a lower dose and have better antihyperglycemic activity than the other antidiabetic drugs metformin or fenofibrate. FAS enzyme regulates the fatty acid synthesis while PPARγ enzyme ligands extensively reduce the blood triglyceride level in dyslipidemia condition. Dehydroeburicoic acid inactivates both the enzymes also enhances CPT-1 an mRNA level which causes β-oxidation to lower TG level in the liver. The serum hypolipidemic activity in the CF1 male mice was investigated for sesquiterpene lactones; Helenalin, inulin, 2,3-epoxytenulin, isotenulin, 2-3 epoxyisotenulin, deoxyelephantopin, eupahyssopin and thymine lactone lowers more than 30% of serum cholesterol level in mice and suppresses triglyceride level. The in-vitro enzyme assay tested for sesquiterpene lactones effectively reduces acetyl-CoA synthetase activity and citrate lyase activity. It inhibits acetyl- CoA carboxylase which participates in fatty acid synthesis. As comparing with standard drug clofibrate requires high dose to lower cholesterol level in rodent where sesquiterpene lactone show very low dose effective for lowering cholesterol and triglyceride level in the rodent. The major moieties of sesquiterpene lactones α-methylene-γ-lactone moiety, β-unsubstituted cyclopentenone ring and α-epoxy cyclopentanone possess antihyperlipidemic activity but in 2,3-dihydrohelenalin,2,3-dihydrotenulin and 2,3-dihydroisotenulin compound the saturation of double bond in cyclopentanone ring at 2,3 position leads to loss of antihyperlipidemic activity. The triglycerides are converted into mono, diglycerides, fatty acids and glycerol by lipase enzyme. The lipase enzyme also hydrolyses some essential lipoproteins (high-density lipoprotein) so to reduce the triglyceride and free fatty acids and to increase HDL level there is a need for inhibition of pancreatic lipase enzyme. The di-terpenoids present in roots of *C.procera* was investigated for having pancreatic lipase inhibition activity. It was discovered that the

cyclic diterpenes phenol,2,4-bis (1,1-dimethyl ethyl) ester and 1,2-benzedenedicarboxylic acid, bis (2-methyl propyl) ester extracted from the roots of C.procera had a higher IC50 value when compared to the positive control group and the inhibition of pancreatic enzyme by constant (Ki) of crude extract, purified diterpenes, and Orlistat.The terpenoids present in the essential oil of Lime were studied to having hypolipidemic activity in Lipid-induced hyperlipidemia in a rat model. The GC study revealed that lime essential oil contains monoterpenes, sesquiterpenes, terpene alcohols, terpene aldehydes, terpene esters and terpene ketone. The maximum per cent of compound present in oil was limonene and others were γ-terpinene, β-pinene, α -pinene and low content of neryl acetate and sabinene. The present compound study also conducted to check antioxidant activity. The hypolipidemic activity study observed improved fatty infiltration with hepatocyte vesicles and inhibits LDL level by showing effective anti-hyperlipidemic action[18].

3. **Reduction in oxidative stress by terpenes:** [18]

The generation of reactive oxygen species plays a major role in the development of diabetes stated by brown lee (2001) which affiliate imbalance in the antioxidant defence system of the human body. Hyperglycemic condition highly produces reducing equivalents NADH and FADH also enhances citric acids cycle flux by electron exchange by these process superoxide anions generate. Impairment in the regulation of neurohumoral like angiotensin II may lead to the release of mitochondrial superoxide. The essential oil extracted from the plant of *Hertia cheirifolia L.* which is rich in terpenes compounds. The high content of α-pinene presents up to 3/4$^{th}$ percent. *Hertia cheirifolia L*. plant is used to lower hyperglycaemia and investigated to having antioxidant activity by invitro DPPH free radical scavenging assay, reducing power and β-Carotene-linoleic acid method. The presence of terpenoids (hydroxylated compounds) provides higher radical scavenging property. The essential oil shows strong inhibition activity at very low IC50 value. It also helps in the reduction of ferric iron to ferrous iron and has lower IC50 value than standard drug butylated hydroxytoluene specifies better inhibition of lipid peroxidation activity. The leaf extract of *J. phoenicea* collected as essential oil containing terpenoid compounds (α-pinene, D-3-carene, Germacrene-D 11, Germacrene-B, limonene, α-cadinene. The ability of free radical- scavenging activity checked by DPPH assay method and β-carotene method and it resulted in methanolic extract showed the strongest free radical scavenging property at low concentration. The redox property of phenolic compounds makes them reducing agent (hydrogen donor) for quenching singlet oxygen. The essential oil of *J. phoenicea* proved to have better inhibition activity against linoleic acid (β-carotene assay) as it contains hydroxylated terpenoid compounds (α-pinene and D-3-carene) [19].

4. **Anti-hyperglycemic activity/ Hypoglycemic activity:** [19]

Diabetes is a metabolic disease caused by long-term increasing blood glucose level and leads to chronic dysfunction of major organs like heart; kidney etc. forskolin diterpene shows potent antidiabetic activity and antihyperlipidemic action in STZ -induced diabetic group. The signalling pathway of β-cells gets activated and enhances the glucose-mediated insulin release which primarily gives hypoglycemic action by forskolin. Also regains lipid profile and glycogen level in the liver to normal. The antidiabetic activity of *Elephantopus scaber L.* has reported earlier and the histological study was conducted to the effect on β-cells of in diabetes-induced rat. The terpenoids revealed to have hypoglycemic and β-cell generation activity. Also, terpenoid of *Elephantopus scaber L.* docked with Peroxisome Proliferator-Activated Receptor-γ (PPARγ: 2PRG) showed greater binding affinity than standard drug Rosiglitazone[20]. Pentacyclic acid triterpenoids (Ursolic acid, Oleanolic acid, Moronic acid, Morolic acid) have significant antidiabetic activity by reducing the plasma glucose level in STZ-induced diabetic rats and also enhances insulin release by translocating insulin-sensitive- cell lines such as glucose transporter 4 in 3T3- L1(27). The essential oil obtained from *Boenninghausenia albiflora* (Hook.) mainly contains monoterpenes, sesquiterpenes, ketones, alcohol and ester. The essential oil possesses hypoglycaemic activity at both high to low concentration which is better than positive control group Glibenclamide. The

mechanism behind the study that essential oil mediates insulin release by sensitizing insulin receptors and cause sugar uptake by tissue. The hypoglycemic activity may be due to β-linalool present in the essential oil of *Boenninghausenia albiflora* (Hook.) is also effective against hepatotoxicity by reducing the alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline Phosphatase, bilirubin, lactate dehydrogenase and influences antioxidant system in the body[21]. The ethanolic extract of *Euphorbia antiquorum Linn.* Possess anti-hyperglycemic activity of treatment at 8th hr. it rises which is remarkable compared with standard drug Glibenclamide[22].

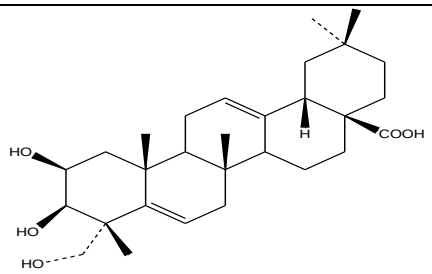
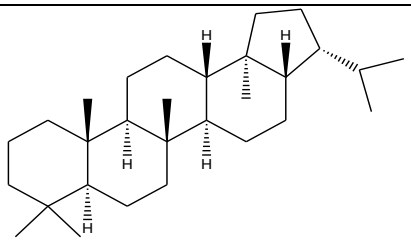
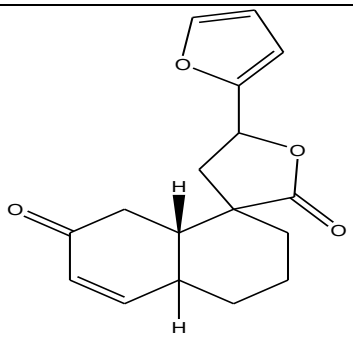
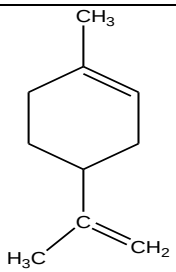
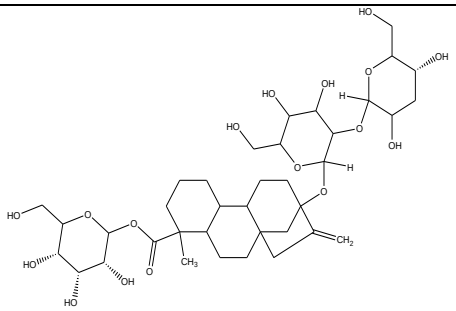
5. **Inhibition of Aldose reductase by terpenes:** [23]

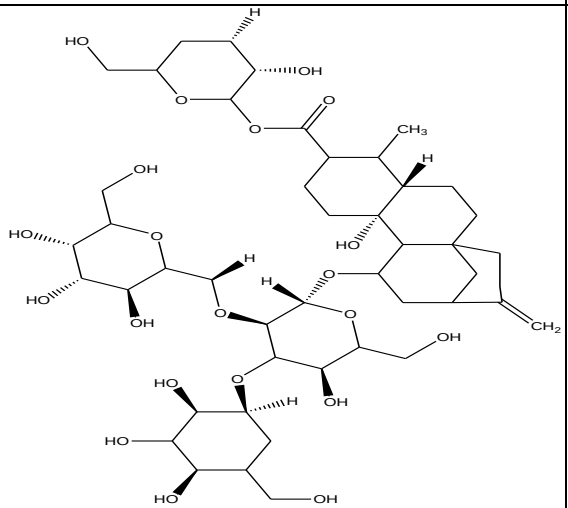
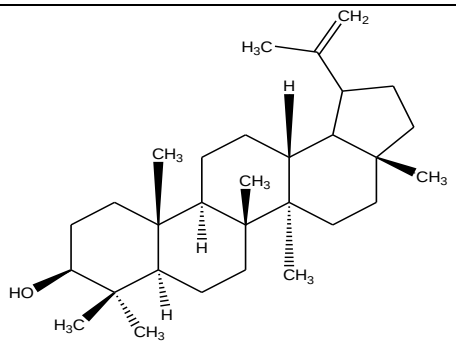
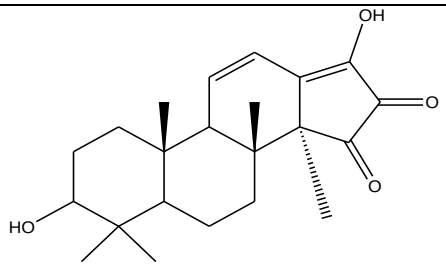
Oxidative stress is the major reason behind the secondary complications in type 2 diabetes, which may arise by auto-oxidation of glucose or by polyol i.e., reduction of glucose to sorbitol by aldose reductase enzyme. This reaction causes the excessive formation of intracellular reactive oxygen species (ROS) in heart, kidney, eyes and other organ tissues such as vasculature, neurons etc. The high glucose level in blood leads to activation of the aldose reductase enzyme. It catalyzes the reduction reaction from glucose to sorbitol and further to fructose by the enzyme fructose dehydrogenase. The polar sorbitol unable to cross the cell membrane and leads to intracellular accumulation which interferes normal cell function, so inhibition of Aldose reductase reduces the secondary complications in chronic metabolic diseases [24]Some medicinal plants have major acceptability to treat diabetes, the extract of *Euphorbia antiquorum Linn.* Containing three triterpenoids Antiquol A, Antiquol B and Antiquol C was evaluated for antidiabetic activity and Insilco AR inhibition activity. The docking study revealed that antiquol A has an effective binding affinity to AR with high glide score than the standard drug Zopolrestat. The triterpenoid Antiquol A shows interaction at asp 160 linked by a hydrogen bond to the C3 carbonyl carbon of AR than the other two triterpenoids[25]. The number of triterpenoids isolated from the fruiting body of *Ganoderma lucidum* shows disclosing bioactive actions in various chronic diseases. The extract of *Ganoderma lucidum* contains 7 triterpenoid compounds lanostane triterpenes (4) and farnesyl hydro-quinone conjugate of triterpenes. The study revealed that lucidumol a triterpenoids exhibited significant inhibition of Aldose reductase comparing to standard Epalrestat. The reaction rate of lucidumol A with AR determined by Lineweaver-Burk and Dixon plots with competitive inhibitors of AR [26]. The various triterpenoids extracted from the stem of *Salacia chinensis* among them oleanane -type triterpenoids (3β,22β-dihydroxyolean-12-en-29-oic acid and maytenfolic acid) and Norfriedelane – type triterpenes (tingenone, tingenin B, regeol A, triptocalline A, and mangiferin) proved to have inhibition against rat lens Aldose reductase enzyme[27].

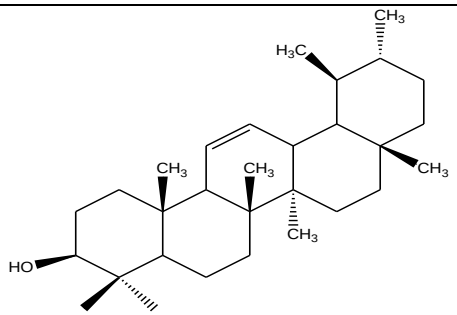
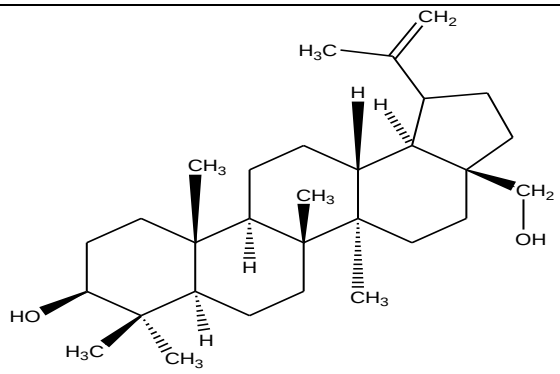
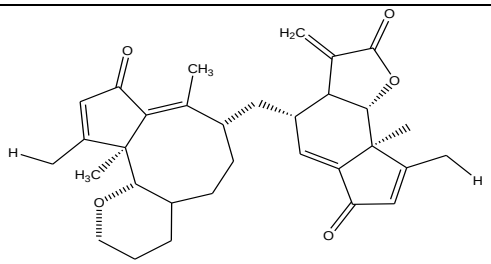
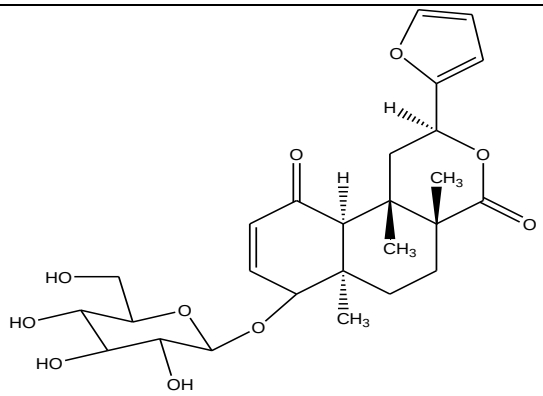
6. **Terpenes as AR inhibitor**[28]

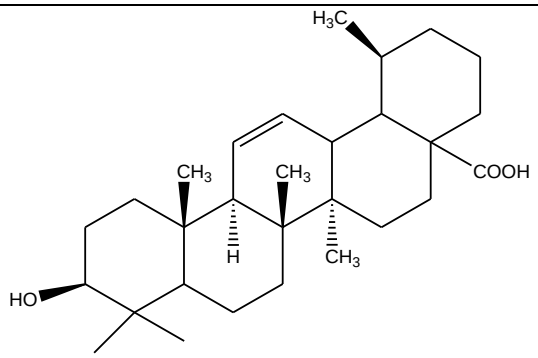
The first enzyme in the polyol pathway, AR, catalyses NAPDH-dependent carbonyl compound reduction, which promotes the development of diabetes complications [29]. AR inhibitors appear to have the potential to slow or stop the advancement of certain long-term diabetes consequences. Salasones A, B, and C, as well as friedelanetype triterpene, salaquinone A, acylated eudesmanetype sesquiterpene, salasol A, and Abietanetype diterpenoids, danshenolsA and B, isolated from the roots and rhizome of *Salvia miltiorrhiza*, have exhibited inhibitory effects on AR found in rat lens. In STZ-induced diabetic mice, the novel colean13enetype triterpene and centellasapogenol A isolated from the methanolic extract of *Centella asiatica* inhibited AR, whereas D-limonene, a natural monocyclic monoterpene, inhibited AR activity and delayed the formation of diabetic cataracts [30].

**Table 1 .Characterized terpenes from plants with their mode of action** [31-40]

| Terpene | Structure | Source | Effect |
|---|---|---|---|
| Bassic acid |  | Root bark of *Bumelia sartorum*[31] | Hypoglycemic, Enhanced secretion of insulin |
| Triterpenes |  | *Salacia hainanensis*[32] | AR inhibitor |
| Trans-Dehydrocrotonin |  | Bark of *Croton cajucara*[33] | Hypoglycemic |
| D-limonene |  | Citrus Fruits[34] | Decrease plasma glucose, increase activity of glycolytic enzymes |
| Stevioside |  | Leaves of *Stevia rebaudiana*[35] | Antihyperglycemic, Insulinotropic, Glucagonostatic |

| | | | |
|---|---|---|---|
| Rebaudioside |  | Leaves of *Stevia rebaudiana*[36] | Insulinotropic |
| Lupeol |  | Mango[37] | Decrease oxidative stres |
| Palbinone |  | *Moutan Cortex*[38] | Induce glucose uptake via AMPK pathway |

| | | | |
|---|---|---|---|
| α-Amyrin |  | Roots of *Ficus bengalensis*[38] | |
| Betulin |  | Root bark of *Euclea undulata*[39] | α-glucosidase inhibition |
| Lactucain A |  | *Lactuca indica*[40] | Lowering of plasma glucose |
| Tinosporaside |  | Ethnaolic extracts of *Tinospora cordifolia* | Anti-hyperglycemic |

| | | | |
|---|---|---|---|
| Urosolic acid |  | Leaves of *Rosmarinus officinalis* | Anti-hyperglycemic |



## EFFECT OF TERPENES ON OTHER COMPLICATIONS OF DIABETES

Triterpenes prevent the formation of AGEs, which are produced during the pathogenesis of diabetic nephropathy, embryopathy, neuropathy, or impaired wound healing In STZ-induced diabetic rats, palbinone, a triterpene, effectively reduced retinal inflammation and oxidative stress caused by high glucose levels[41]. During diabetic retinopathy, it also activated the antioxidative Nrf2 pathway and inhibited the formation of NLRP3 inflammasomes. In STZ diabetic mice, oleanolic acid and ursolic acid inhibited renal AR activity. It also increases glyoxalase I activity, resulting in decreased renal AGE formation and improved renal functions. Ursolic acid protected the kidneys of type 2 diabetic db/db mice. By downregulating proteins in the ARAp1/AT1R signal pathway, it also inhibits extracellular matrix accumulation, renal inflammation, and oxidative stress[42]. In another study, ursolic acid increases SIRT1 overexpression, resulting in cell regeneration in STZ-induced diabetic mice. Terpene glycoside component of *Paeonia suffruticosa* root bark Furthermore, inhibiting IRE1/NF-kB activation improved ER stress-related inflammation in the pathogenesis of diabetic nephropathy. In STZ-NA induced diabetic mice, betulinic acid significantly reduced liver damage by improving leptin, adiponectin, liver enzyme levels, and lipid profile. Eugenol, a component of clove oil, reduced vascular and neural complications in Sprague-Dawley rats. The observed activity was linked to eugenol's anti-oxidant and anti-inflammatory properties. In STZ-induced diabetic rats, zerumbone, a sesquiterpene, improves retinal damage by blocking AGEs and their receptor system. . By inhibiting the p38 MAPK and NF-kB signalling pathways, it reduces the severity of retinal inflammation and angiogenesis[43].

## TERPENES AGAINST SOME NOVEL THERAPEUTIC TARGETS

Insulin binding to IR causes phosphorylation of IRS, which mediates glucose transport into the cell and glycogen synthesis [44]. PTP1B is an intracellular protein that dephos phorylates tyrosine residues to negatively regulate the insulin and leptin signalling pathways PTP1B mediates. As a result of blocking negative insulin and leptin signals, inhibiting may improve insulin sensitivity. Terpenes and terpenoids isolated from plants inhibited the PTP1B protein effectively. PTP1B enzymes were significantly inhibited by diterpenes from the soft coral *Sarcophyton trocheliophorum* and triterpenoids from *Cedrela odorata*. Diterpenes isolated from a chloroform extract of the roots of *Acanthopanax koreanum* inhibited PTP1B in a dose-dependent manner in another study. Two new diterpenes isolated by bioassay-guided fractionation from the aerial parts of *Siegesbeckia glabrescens* inhibited PTP1B protein in a non-competitive manner[45]. Pentacyclic triterpenoids isolated from the stem bark of *Styrax japonica* inhibited PTP1B as well. GLP 1 and other incretin hormones play an important role in blood glucose regulation. DPP IV is a serine peptidase that rapidly degrades incretin hormones, resulting in the enzyme's short life span. By inhibiting DPP IV, the endogenous level of GLP 1 is maintained, resulting in increased glucose secretion and cell mass. The ethanolic extract of Urena lobata leaves inhibited DPP IV more

effectively, with an IC50 value of 1654.64 g/mL. The presence of terpenoid compounds was responsible for the activity, as revealed by LC-MS and an in silico docking study. According to molecular docking, Rebaudioside A and Stevioside, two sesquiterpene glycosides from *Stevia rebaudiana*, inhibit DPP-IV. Similarly, a pentacyclic terpene derived from chloroform extracts of I. obliquus mycelium powders was predicted to have DPP IV inhibitory activity based on a molecular docking study PPAR is a nuclear receptor superfamily member that regulates the gene expression of proteins involved in glucose and lipid control [46]. Two dietary terpenoids, Bixin and Norbixin, activated PPAR to regulate carbohydrate and lipid metabolism in KK-AY obese mice. Bixin also stimulated adipocyte differentiation and insulin-stimulated glucose uptake in 3T3-L1 adipocytes by inducing PPAR genes. The diterpene compounds found in rosemary and sage extracts, carnosol and carnosic acid, have been shown to lower blood glucose levels while also activating PPAR in a dose-dependent manner. Furthermore, various dietary terpenes have been shown to modulate PPAR, which is beneficial in the treatment of obesity-induced type II diabetes [47].

## MISCELLANEOUS EFFECTS OF TERPENES

In another study, oral administration of Dlimonene decreased plasma glucose, glycosylated hemoglobin levels, activities of gluconeogenic enzyme-like glucose 6-phosphatase and fructose 1, 6 bisphosphatase with activated activity of glycolytic enzyme, glucokinase, and liver glycogen in diabetic mice[48]. Announced Result of Dlimonene was detected at a body weight of 100 mg / kg and is compared to glibenclamide. A portion of triterpene acid (TTA) from the leaves Eriobotrya japonica has shown hypoglycemic as well hypolipidemic effect on both alloxan and STZ-induced diabetes mice. The effective oral dose of TTA (300 mg / kg) is reduced GSP, TC, and TG levels in high-sugar mice. In addition, SOD activity and serum insulin levels of dia betic mice were also increased. Terpenoid, palbinone separated from the Moutan cortex (*Paeonia suffruticosa, Paeoniaceae*) strongly promoted AMPK, GSK3β, and ACC phosphorylation in HepG2 cells under high glucose to focus. It also took up the absorption of glucose and glycogen. In another study, oral administration of Dlimonene de creased plasma glucose, glycosylated hemoglobin levels, activities of gluconeogenic enzyme-like glucose 6-phosphatase and fructose 1, 6 bisphosphatase by activated glycolytic enzyme, glucokinase, and liver glycogen in diabetic mice. Announced Result of Dlimonene was found to weigh 100 mg / kg and is compared to glibenclamide[49]. Part of triterpene acid (TTA) from the leaves Eriobotrya japonica has also shown hypoglycemic hypolipidemic effect on both alloxan and STZ-mice mice. The effective oral dose of TTA (300 mg / kg) decreases Level of GSP, TC, and TG in high-sugar mice.In addition, SOD activity and serum insulin levels of diabetic mice were also increased. Terpenoid, palbinone separated from the Moutan cortex (Paeonia suffruticosa, Paeoniaceae) strongly recommended AMPK, GSK3β, and Ph phosphorylation in HepG2 cells under high glucose to focus. It also absorbed glucose and glycogen absorption synthesis in a volume-dependent manner, showing an important role in the formation of glucose metabolism in the form of AMPK. Sesquiterpene lactone from *Foeniculum vulgare* regulates NF-kB and MAPK pathways.Costunolide (sesquiterpene separated from Costus speciosus) lowered serum total cholesterol, tri glyceride, LDL cholesterol increasing simultaneously plasma insulin, glycogen tissue, HDL cholesterol and serum protein [50].

## TERPENES IN CLINICAL TRIALS WITH POTENTIALLY ANTI-DIABETIC ACTIVITY

Searching for a new drug is only possible after the clinic case. Upon completion of the clinical trial, the applicant uploads the New Drug Application (NDA) with FDA or Marketing.Application for Authorization (MAA) and EMEA to seek drug drug marketing in the US and Europe carefully Here are some of the results of clinical trials which included the antidiabetic effect of terpenes was discussed[51]. In two random groups of 12 patients, 150 mg of Ursolic acid (a pentacyclic triterpenoid with car boxylic acid) was given for 12 weeks to study the effect of insulin sensitivity and metabolic syndrome. In another study, it did have been shown to reduce adipogenesis and the percentage of body fat by simultaneous increase in muscle mass in rat models such as and to

human volunteers. These are therapeutic temptations indicate that terpenes may also appear effective treatment for diabetes. Aside from a lot of chemical data on the anti-diabetic properties of terpenes, there lack of clinical studies and trials on terpenes. Preclinical too human physiology studies have shown the use of terpenes to diagnose diabetes[52]. But it has to be established by clinical testing for terpenes to deliver as a potent anti-diabetic molecule on the market. For many promising data in early and prenatal studies, terpenes have now to prove their effectiveness and safety more randomly controlled trials. Terpenes should be considered in other clinics usability and safety lessons to prove their claim to an antidepressant drug which is the most common modern requirement with new diabetes treatment options [53].

## STRUCTURE-ACTIVITY RELATIONSHIP OF TERPENES

The molecular structure of terpenes plays a major role in demonstrating its function. Sesquiterpenoids are very effective in treating diabetes due to compound cell formation, low ramification, and low dosage. Triterpenes, on the other hand, contain hydroxyl and carboxyl groups that have great potential in treating diabetes with a variety of mechanisms. Terpenes with high hydrogen bonds and hydrophobic interactions can also increase the anti-diabetic activity of terpenes[54].

## PHARMACOLOGY, SHORTCOMINGS, AND FUTURE PERSPECTIVES OF TERPENES

Terpenes have well-known medicinal properties and excellent biological activity. Camphor oil and terpenes are the most well-known compounds in this group and work well on many problems. The results mentioned above support the great potential of terpenes in the treatment of diabetes[55]. The terpene compounds are easily absorbed by the body after skin transplantation due to its lipophilic nature. But a few studies reported the absorption of terpenes after oral ingestion. Therefore, a better understanding of the absorption of the included terpenes is necessary to maximize its therapeutic efficacy. In a recent study, terpene developed by SLN and NLC showed higher skin availability that enhanced their dermal drug delivery capacity. Terpenes are synthesized with cytochrome P450 and released by the kidneys as synthetic metabolites[56]. Very little detail is available on the medicinal properties of terpenes. Detailed pharmacokinetic parameters (absorption, metabolism, distribution, elimination) of terpenes also need to be considered for its safety tests. Significant activity on terpenes is required in the study of various medical parameters. Before emphasizing terpenes as a powerful anti-diabetic, it is also necessary to discuss its various flaws of terpenes including: the beliefs associated with terpenes, contradict its use as a pharmaceutical drug, (iii) lack of pharmacokinetics and pharmacodynamics data, (iv) hepatic / renal system problem in overuse, (v) rapid rate of immunosuppression, , (vii) There may be many ingredients, (viii) the delivery system for a specific target is generally not guaranteed, and (ix) lack of standards. Problems and shortcomings are often associated with research work. But solutions to such limitations of terpenes should be weighed before its commercial use, which includes monitoring terpene bioprospection, extraction, and separation of bio-activity activities using existing technological standards. This process still poses challenges such as potential identification, toxicity testing, and a lack of defined rules. But other studies are being confirmed to ensure that the appropriate methodology for developing future research goals attempts at terpenes in a more focused way. Small amount of data is used and tested in a terpenes clinical trial. Therefore, the focus should be on clinical trials of purified terpenes. It would be a good step forward in acquiring terpenes as a drug that could treat diabetes and be able to fill the void of diabetes science [57]. Therefore, better methods should be enforced to improve terpene yields[58]. Terpenes from different sources have shown different effects, so the variability of line structure in different natural products should be tested to better understand how it works of action [59]. The current literature focuses exclusively on the common purposes of terpenes, namely, inhibition of carbohydrate enzymes, lowering blood glucose, and reducing oxidative stress [60]. The impact of terpenes on new targets (DPP-IV, PTP1B) should also be investigated further and highlighted in future research[61].

**CONCLUSION:**

The review is based on literature available on terpenes, which has highlighted the future role of terpenes as a natural anti-diabetic agent. The treatments available for diabetes are unsatisfactory and fail to work for all patients. Terpenes from various sources reported as hypoglycemic, hypolipidemic, αglucosidase inhibitor, etc. In short, it also lowers blood glucose and oxidative stress, thus preventing diabetic complications. Terpenes also reduce body fat and other side effects from common anti-diabetic drugs. They are economical and environmentally friendly and show strong antidiabetic activity in in vitro and in vivo studies. These terpenes have been reported, although they show anti-diabetic effects, but have not yet been tested in clinical studies. Untested terpenes should be subjected to medical studies in order to be effective, strong, and safe to confirm their clinical status. Some terpenes are in clinical trials and produce good results. However, further research is needed to develop the goals of terpene compounds increase its therapeutic efficacy diabetes. In conclusion, enough scientific evidence was gathered in this review supports plant-based terpenes as an effective and safe lead molecule for drug development against diabetes. The bio-produced terpenes could be the future molecule beneficial treatment of hyperglycemia and prevention of diabetes complications. Therefore, the establishment of terpenes as a scientifically approved drug for Diabetes requires the adoption of effective goal setting strategies, appropriate research, and clinical research to have confirmed its effectiveness in human use.

**REFERENCES:**

1. Jasmine R, Kumar GA. Probing the mechanism of the anti-diabetic potential of a terpenoid from elephantopus scaber L an Indian ethnomedicinal plant in STZ diabetic rats- in vivo and in silico analysis*. **Indian J Biochem Biophys***. 2018.55(6):384–8.
2. Panigrahy SK, Bhatt R, Kumar A. Targeting type II diabetes with plant terpenes: the new and promising antidiabetic therapeutics. ***Biologia (Bratisl)***. 2021.76(1):241–54.
3. Habtemariam S. Antidiabetic potential of monoterpenes: A case of small molecules punching above their weight. ***Int J Mol Sci***. 2018.19(1):1–23.
4. Yang W, Chen X, Li Y, Guo S, Wang Z, Yu X. Advances in Pharmacological Activities of Terpenoids. ***Nat Prod Commun***. 2020.15(3):140-150
5. Ludwiczuk A, Skalicka-Woźniak K, Georgiev MI. Terpenoids. Pharmacognosy: Fundamentals, ***Applications and Strategy***. 2017.14(2): 233–266.
6. Castellano JM, Guinda A, Delgado T, Rada M, Cayuela JA. Biochemical basis of the antidiabetic activity of oleanolic acid and related pentacyclic triterpenes. ***Diabetes.*** 2013.62(6):1791–1799.
7. Basak SS, Candan F. Chemical composition and in vitro antioxidant and antidiabetic activities of Eucalyptus camaldulensis Dehnh. essential oil. ***J Iran Chem Soc***. 2010.7(1):216–26.
8. Keskes H, Mnafgui K, Hamden K, Damak M, El Feki A, Allouche N. In vitro anti-diabetic, anti-obesity and antioxidant proprieties of Juniperus phoenicea L. leaves from Tunisia. ***Asian Pac J Trop Biomed***. 2014.4( 2):649–655.
9. Etsassala NG, Badmus JA, Waryo TT, Marnewick JL, Cupido CN, Hussein AA, et al. Alpha-glucosidase and alpha-amylase inhibitory activities of novel abietane diterpenes from Salvia Africana-Lutea. ***Antioxidants.*** 2019.8(10):1–12.
10. Sabitha V, Ramachandran S, Naveen KR, Panneerselvam K. Antidiabetic and antihyperlipidemic potential of Abelmoschus esculentus (L.) Moench. in streptozotocin-induced diabetic rats. ***J Pharm Bioallied Sci***. 2011.3(3):397–402.
11. Kuo YH, Lin CH, Shih CC. Antidiabetic and Antihyperlipidemic Properties of a Triterpenoid Compound, Dehydroeburicoic Acid, from Antrodia camphorata in Vitro and in Streptozotocin-Induced Mice. ***J Agric Food Chem***. 2015.63(46):10140–10151.
12. Hall IH, Lee KH, Starnes CO, Muraoka O, Sumida Y, Waddell TG. Antihyperlipidemic activity of sesquiterpene lactones and related compounds. **J *Pharm Sci***. 1980.69(6):694–7.
13. Patil SG, Patil MP, Maheshwari VL, Patil RH. In vitro lipase inhibitory effect and kinetic properties of di-terpenoid fraction from

Calotropis procera (Aiton). ***Biocatal Agric Biotechnol***. 2015.4(4):579–85.
14. Lin LY, Chuang CH, Chen HC, Yang KM. Lime (Citrus aurantifolia (Christm.) swingle) essential oils: Volatile compounds, antioxidant capacity, and hypolipidemic effect, ***Foods***. 2019.8(9):41-51
15. Fakhruddin S, Alanazi W, Jackson KE. Diabetes-Induced Reactive Oxygen Species: Mechanism of Their Generation and Role in Renal Injury. ***J Diabetes Res***. 2017.4(3):10-15
16. Schaffer SW, Azuma J, Mozaffari M. Role of antioxidant activity of taurine in diabetes. ***Can J Physiol Pharmacol. 2009***.87(2):91–9.
17. Shahzadi P. In Vivo Hepatoprotective and Antidiabetic Activities of Essential Oils from Boenninghausenia albiflora (Hook.) Reichb. Ex Heynkh, of Pakistan. ***MOJ Bioequivalence Bioavailab***. 2017.4(1):22-28.
18. Morikawa T, Kishi A, Pongpiriyadacha Y, Matsuda H, Yoshikawa M. Structures of new friedelane-type triterpenes and eudesmane-type sesquiterpene and aldose reductase inhibitors from Salacia chinensis. ***J Nat Prod***. 2003.66(9):1191–6.
19. Galle M, Crespo R, Rodenak Kladniew B, Montero Villegas S, Polo M, De Bravo MG. Suppression by geraniol of the growth of A549 human lung adenocarcinoma cells and inhibition of the mevalonate pathway in culture and in vivo: Potential use in cancer chemotherapy. ***Nutr Cancer***. 2014.66(5):888–95.
20. Carnesecchi S, Bradaia A, Fischer B, Coelho D, Gosse F. Perturbation by geraniol of cell membrane permeability and signal transduction pathways in human colon cancer cells. ***J Pharmacol Exp Ther***. 2002.303(2):711–5.
21. Burke YD, Stark MJ, Roach SL, Sen SE, Crowell PL. Inhibition of pancreatic cancer growth by the dietary isoprenoids farnesol and geraniol***. Lipids.*** 1997.32(2):151–6.
22. Araujo AA, Duarte MC, Gelain DP, Moreira JCF. Structure-activity relationship of terpenes with anti-inflammatory profile - A systematic review. ***Basic Clin Pharmacol Toxicol***. 2014.115(3):244–56.
23. Guimarães AC, Meireles LM, Lemos MF, Guimarães MCC, Endringer DC, Fronza M. Antibacterial activity of terpenes and terpenoids present in essential oils. ***Molecules***. 2019.24(13):1–12.
24. Boukhatem MN. Effective Antiviral Activity of Essential Oils and their Characteristics Terpenes against Coronaviruses: An Update. ***J Pharmacol Clin Toxicol***. 2020.8(1138):1–8.
25. San Dagli Gul A, Fadillioglu E, Karabulut I, Yesilyurt A, Delibasi T. The effects of oral carvacrol treatment against $H_2O_2$ induced injury on isolated pancreas islet cells of rats. Islets. 2013.5(4):149–55.
26. Joglekar MM, Panaskar SN, Arvindekar AU. Inhibition of advanced glycation end product formation by cymene - A common food constituent. ***J Funct Foods***, 2014.6(1):107–115.
27. Ma CJ, Nie AF, Zhang ZJ, Du ZGZ, Li XY, Ning G. Genipin stimulates glucose transport in C2C12 myotubes via an IRS-1 and calcium-dependent mechanism. ***J Endocrinol***. 2013.216(3):353–62.
28. Guan L, Feng H, Gong D, Zhao X, Cai L, Wu Q. Genipin ameliorates age-related insulin resistance through inhibiting hepatic oxidative stress and mitochondrial dysfunction. ***Exp Gerontol***. 2013.48(12):1387–1394.
29. Zhang Y, Ding Y, Zhong X, Guo Q, Wang H, Gao J. Geniposide acutely stimulates insulin secretion in pancreatic β-cells by regulating GLP-1 receptor/cAMP signaling and ion channels. ***Mol Cell Endocrinol***.2016.430:89–96.
30. Zhang L, Yang B, Yu B. Paeoniflorin protects against nonalcoholic fatty liver disease induced by a high-fat diet in mice. ***Biol Pharm Bull***. 2015.38(7):1005–11.
31. Zhang Y, Yin F, Liu J, Liu Z, Guo L, Xia Z. Geniposide attenuates insulin-deficiency-induced acceleration of β-amyloidosis in an APP/PS1 transgenic model of Alzheimer's disease. ***Neurochem Int***. 2015.89:7–16.
32. Wu SY, Wang GF, Liu ZQ, Rao JJ, Lü L, Xu W. Effect of geniposide, a hypoglycemic glucoside, on hepatic regulating enzymes in diabetic mice induced by a high-fat diet and streptozotoci. ***Acta Pharmacol Sin***. 2009.30(2):202–8.
33. Guo LX, Liu JH, Yin F. Regulation of insulin secretion by geniposide: Possible involvement of phosphatidylinositol 3-

phosphate kinase. ***Eur Rev Med Pharmacol Sci***. 2014.18(9):1287–94.
34. Kojima K, Shimada T, Nagareda Y, Watanabe M, Ishizaki J, Sai Y. Preventive effect of geniposide on metabolic disease status in spontaneously obese type 2 diabetic mice and free fatty acid-treated HepG2 cells. ***Biol Pharm Bull***. 2011.34(10):1613–8.
35. Kong P, Chi R, Zhang L, Wang N, Lu Y. Effects of paeoniflorin on tumor necrosis factor-α-induced insulin resistance and changes of adipokines in 3T3-L1 adipocytes. ***Fitoterapi***. 2013.91:44–50.
36. Jiang B, Qiao J, Yang Y, Lu Y. Inhibitory effect of paeoniflorin on the inflammatory vicious cycle between adipocytes and macrophages. ***J Cell Biochem***. 2012.113(8):2560–2566.
37. Sun X, Li S, Xu L, Wang H, Ma Z, Fu Q, et al. Paeoniflorin ameliorates cognitive dysfunction via regulating SOCS2/IRS-1 pathway in diabetic rats. ***Physiol Behav***. 2017.174:162–169.
38. Saravanan S, Pari L. Role of thymol on hyperglycemia and hyperlipidemia in high fat diet-induced type 2 diabetic C57BL/6J mice. ***Eur J Pharmacol***. 2015.761:279–287.
39. Kodikonda M, Naik PR. Ameliorative effect of borneol, a natural bycyclic monoterpene against hyperglycemia, hyperlipidemia and oxidative stress in streptozotocin-induced diabetic Wistar rats. ***Biomed Pharmacother***. 2017.96:336–47.
40. Murali R, Saravanan R. Antidiabetic effect of d-limonene, a monoterpene in streptozotocin-induced diabetic rats. ***Biomed Prev Nutr***.2012.2(4):269–75.
41. Muruganathan U, Srinivasan S, Vinothkumar V. Antidiabetogenic efficiency of menthol, improves glucose homeostasis and attenuates pancreatic β-cell apoptosis in streptozotocin–nicotinamide induced experimental rats through ameliorating glucose metabolic enzymes. ***Biomed Pharmacother***.2017.92:229–39.
42. Vaidya H, Prajapati A, Rajani M, Sudarsanam V, Padh H, Goyal RK. Beneficial effects of swertiamarin on dyslipidaemi in streptozotocin- induced type 2 diabetic rats. ***Phyther Res.*** 2012.26(8):1259–61.
43. Venkatachalapathi A, Thenmozhi K, Karthika K, Ali MA, Paulsamy S, AlHemaid F. Evaluation of a labdane diterpene forskolin isolated from Solena amplexicaulis (Lam.) Gandhi (Cucurbitaceae) revealed promising antidiabetic and antihyperlipidemic pharmacological properties. ***Saudi J Biol Sci***. 2019;26(7):1710–5.
44. Badmaev V, Hatakeyama Y, Yamazaki N, Noro A, Mohamed F, Ho CT, et al. Preclinical and clinical effects of Coleus forskohlii, Salacia reticulata and Sesamum indicum modifying pancreatic lipase inhibition in vitro and reducing total body fat. ***J Funct Foods***. 2015.15:44–51.
45. Huang PK, Lin SR, Riyaphan J, Fu YS, Weng CF. Polyalthia clerodane diterpene potentiates hypoglycemia via inhibition of dipeptidyl peptidase 4. ***Int J Mol Sci***. 2019;20(3).
46. Abhijeet SK, Kelly R, Balaji R, and Russell GK. A halogenated pseudopterane diterpene from the Bahamian octocoral Pseudopterogorgia acerosa, ***Can. J. Chem.*** 2010.88(4): 318–322.
47. Abourashed EA, Ganzera M, Khan IA, Khan S, Mossa JS, Feraly FS. HPLC fingerprinting and estimation of the bioactive components of Clutia richardiana L. as a potential hypoglycemic herbal tea, ***Phytotherapy Research***.2003.17 (6), 657-60.
48. Abudula R, Jeppesen PB, Rolfsen SD, Xiao J, Hermansen K. Rebaudioside A potently stimulates insulin secretion from isolated mouse islets: Studies on the dose-, glucose-, and calciumdependency, Metabolism: Clinical and Experimental, 2004.53 (10),1378- 81.
49. Adachi H, Kondo T, Ogawa R, Sasaki K, Morino KS, Sakakida M, Kawashima J, Motoshima H, Furukawa N, Tsuruzoe K, Miyamura N, Kai H, and Araki E,. An acylic polyisoprenoid derivative,geranylgeranylacetone protects against visceral adiposity and insulin resistance in high-fat-fed mice, American Journal of Physiology Endocrinology and Metabolism, 2010.299 (5), E764-E71.
50. Ajjan GPJ. The cardiovascular safety of rosiglitazone, ***Expert Opinion On Drug Safety***, 2008.7 (4): 367–76.
51. Ahmed N. Advanced glycation endproducts-role in pathology of diabetic complications. ***DiabetesRes Clin Pract*** .2005.67:3–21
52. Alberts P, Engblom L, Edling N, Forsgren M, Klingstro¨m G, Larsson C. Selective inhibition of 11b-hydroxysteroid

dehydrogenase type 1 decreases blood glucose concentrations in hyperglycaemic mice. ***Diabetologia*** 2002.45.1528–1532.

53. Ali MS, Jahangir M, Hussan SS, Choudhary MI. Inhibition of a-glucosidase by oleanolic acid and its synthetic derivatives. Phytochemistry 2002.60:295–299.
54. Ali H, Houghton PJ, Soumyanath A. α-Amylase inhibitory activity of some Malaysian plants used to treat diabetes; with particular reference to Phyllanthus amarus. ***J Ethnopharmacol*** .2006.107:449–455.
55. Gowri PM, Tiwari AK, Ali AZ, Rao JM. Inhibition of aglucosidase and amylase by bartogenic acid isolated from Barringtonia racemosa Roxb. seeds. ***Phytother Res*** 2007.21:796–799
56. Guan T, Qian Y, Tang X, Huang M, Huang L, Li Y, Sun H () Maslinic acid, a natural inhibitor of glycogen phosphorylase, reduces cerebral ischemic injury in hyper-glycemic rats by GLT-1 up-regulation. ***J Neurosci Res***. 2011.89:1829–1839.
57. Harborne JB, Baxter H. Phytochemical dictionary. A handbook of bioactive compounds from plants. ***Taylor & Francis***,1993.14(6)728–738.
58. Hou W, Li Y, Zhang Q, Wei X, Peng A, Chen L, Wei Y. Triterpene acids isolated from Lagerstroemia speciosa leaves as a-glucosidase inhibitors. ***Phytother Res*** 2009.23:614–618.
59. Huang YC, Chang WL, Huang SF, Lin CY, Lin HC, Chang TC. Pachymic acid stimulates glucose uptake through enhanced GLUT4 expression and translocation. ***Eur J Pharmacol***, 2010.648:39–49
60. Ishijima S, Takashima T, Ikemura T, Izutani Y. Gymnemic acid interacts with mammalian glycerol-3-phosphate dehydrogenase. ***Mol Cell Biochem***.2008.310:203–208.
61. Trojan H, Kopp T, Laszczyk MN, Scheffler A. Pentacyclic triterpene distribution in various plants–rich sources for a new group of multi-potent plant extracts. ***Molecules*** 2009.14:2016–2031.