Abstract. Diabetes mellitus is an independent risk factor for the development of coronary artery diseases, myocardial infarction, hypertension, and dyslipidemia. Clinically diabetic patients are characterized by marked increase in blood glucose level followed by mild hyperlipidemia. Non-insulin dependent diabetes mellitus (NIDDM) accounts for approximately 80–90% of all cases and it is the fastest growing global threat to public health. If the current trend continues, it is likely to result in an estimated 215 million sufferers from NIDDM worldwide by the year 2010. When carbohydrates are in low supply or their breakdown is incomplete, fats become the preferred source of energy. Fatty acids are mobilized into the general circulation leading to secondary triglyceridermia in which total serum lipids in particular triglycerides as well as the levels of cholesterol and phospholipids increases. This rise is proportional to the severity of the diabetes. Uncontrolled diabetes is manifested by a very high rise in triglycerides and fatty acid levels. These conditions are responsible for one third of deaths in industrialized nations. Plants have always been a rich source of drugs and many of the currently available drugs have been derived either from natural products or its templates. We here in present a precise description of naturally occurring compounds possessing potential antihyperglycemic action or antidyslipidemic action against specific drug targets.

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1. Diabetes mellitus

Diabetes is a disease in which the body does not produce or properly use insulin. Insulin is a hormone that converts sugar, starch and other food into energy needed for daily life. The causes of diabetes are not known clearly, although both genetics and environmental factors such as obesity and lack of exercise appear to play roles. Diabetes mellitus and glucose intolerance are common in adolescent and adult patients with cystic fibrosis. Diabetes is invariably associated with pancreatic exocrine dysfunction (malabsorption). The prevalence in patients over 20 years of age may be as high as 53% [1]. The major types of diabetes include type-I and type-II diabetes. The former results from the body's failure to produce insulin, the hormone that "unlocks" the cells of the body, allowing glucose to enter and fuel them while the latter results from insulin resistance, a condition in which the body fails to properly use insulin combined with relative insulin deficiency. Type-II insulin-resistant diabetes mellitus accounts for 90-95% of all diabetes. This heterogeneous disorder afflicts an estimated 6% of the adult population in western society; its worldwide frequency is expected to continue to grow by 6% per annum, potentially reaching a total of 200-300 million cases in 2010 [2].

2. Drug targets

At present, therapy for type-II diabetes relies mainly on several approaches intended to reduce the hyperglycemia itself.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Molecular target</th>
<th>Site(s) of action</th>
<th>Adverse events</th>
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<tbody>
<tr>
<td>Insulins</td>
<td>Insulin receptor</td>
<td>Liver, muscle, fat</td>
<td>Hypoglycemia, weight gain</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>SU receptor/ K+</td>
<td>Pancreatic β-cell</td>
<td>Hypoglycemia, weight gain</td>
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<tr>
<td>(e.g. glibenclamide) plus nateglinide &amp; repaglinide</td>
<td>ATP channel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biguanides</td>
<td>Unknown</td>
<td>Liver (muscle)</td>
<td>Gastrointestinal disturbances, lactic acidosis</td>
</tr>
<tr>
<td>Metformin</td>
<td>α-glucosidase</td>
<td>Intestine</td>
<td>Gastrointestinal disturbances</td>
</tr>
<tr>
<td>Acarbose</td>
<td></td>
<td></td>
<td>Weight gain, anemia, oedema</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>PPARγ</td>
<td>Fat, muscle, liver</td>
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<td>Rosiglitazone, Pioglitazone</td>
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3. Antihyperglycemic isolates from nature

Plants have always been an exemplary source of drugs and many of the currently available drugs have been derived directly or indirectly from them. The ethnobotanical information reports that about 800 plants may possess anti-diabetic potential [3]. Several such herbs have depicted antidiabetic activity while assessed using currently available experimental techniques [4]. A wide array of plant derived active principles representing numerous chemical compounds has demonstrated activity consistent with their possible use in the treatment of non-insulin dependent diabetes mellitus (NIDDM) [5].

Amongst these are flavonoids, alkaloids, glycosides, polysaccharides, peptidoglycans, hypoglycans, guanidine, steroids, carbohydrates, glycopeptides, terpenoids and amino acids. Even the discovery of widely used hypoglycemic drug, metformin was developed on the basis of the natural products lead isolated from *Galega officinalis* [6]. Thus, plants are a potential source of anti-diabetic drugs. Herein, is presented a precise description of naturally occurring compounds possessing potential antihyperglycemic action.

3.1. Flavonoids

The flavonoids are polyphenolic compounds possessing 15 carbon atoms; two benzene rings joined by a linear three carbon chain. flavonoids constitute one of the most characteristic classes of compounds in higher plants. Many flavonoids are easily recognized as flower pigments in most angiosperm families (flowering plants). However, their occurrence is not restricted to flowers but include all parts of the plant. They show wide variety of activities including antihyperglycemic activity. Bio-flavonoids with promising anti-diabetic potential: A critical survey by Goutam Brahmachari will give comprehensive information on the flavonoids and their antihyperglycemic activity.

3.2. Triterpenoids and steroids

There are at least 4000 known triterpenes, which are derived from mevalonic acid pathway. Triterpenes are precursors to steroids in both plants and animals. Steroids are hormonal substances in animals, but they are components of membranes in most organisms. Many triterpenes and sterols occur free, but others occur as glycosides or in special combined forms.

*Momordica charantia* belongs to the family of Cucurbitaceae the fruits of the plant is also known as bitter melon or bitter guard. Cucurbitane class of
triterpenoids isolated from *M. charanta* such as 5-β,19-epoxy-3-β,25-dihydroxy cucurbita-6,23-(E)-diene (1) and 3-β,7-β,25-trihydroxy cucurbita-5,23-(E)-dien-19-αl (2) have blood hypoglycemic effects in the diabetes-induced male ddY mice strain at 400 mg/kg [7].

Hypoglycemic activity guided fractionation together with chemical analysis on the stem of *Agarista mexicana* led to the isolation of 12-ursene (3) and 23,24-dimethyl-24-ethyl-stigmast-25-ene (4) from the chloroform fraction. The isolated triterpenes showed hypoglycemic activity in normal and alloxan-diabetic CD1 mice at a dose of 50 mg/kg body weight. Comparison was made between the action of the triterpenes and a known hypoglycemic drug, tolbutamide (50 mg/kg). The 12-ursene (3) was found to be less potent than tolbutamide where as 23,24-dimethyl-24-ethyl-stigmast-25-ene (4) was shown to be more effective than tolbutamide [8].

From the roots of *Salacia oblonga* a friedelane-type triterpene, kotalagenin 16-acetate (5), maytenfolic acid (6), 3β,22α-Dihydroxyolean-12-en-29-oic acid (7) and a unique thiosugar sulfonium sulfate named Salacinol (60) was isolated. They were screened for inhibitory activity on aldose reductase and were found to be responsible components for the inhibitory activity [9].

Bioassay-guided isolation work on *Cabernet Sauvignon’s* grape skin yielded antihyperglycemic active compounds which were identified as, oleanolic acid (8) and oleanolic aldehyde (9). These compounds were assayed for insulin production using an INS-1 cell assay. In a dose-response study,
Oleanolic acid stimulated insulin production of INS-1 cells by 20.23, 87.97, 1.13 and 6.38 ng of insulin/ mg of protein at a dose of 6.25, 12.5, 25 and 50 μg/mL respectively. The activity was similar to the dose-dependent insulin production of INS-1 cells by glucose. Oleanolic aldehyde also showed a dose-dependent insulin production in the same assay [10]. Our activity guided fractional and isolation work on the plant *Ficus racemosa* yielded moderately active antihyperglycemic principle, α-amyrin acetate (10). Several ester derivatives of α-amyrin were prepared to study their structure activity relationship [11].

Triterpenoid and steroidal glycosides referred to collectively as saponins are bioactive compounds present naturally in many plants and known to possess potent hypoglycemic activity [12]. Glucuronide saponin named betavulgaroside (11) was isolated from the roots and leaves of *Beta vulgaris* L. (sugar beet) exhibited hypoglycemic effect in rats [13].
The root cortex of *Aralia elata* provided another triterpnoid glycoside, Elatoside E (12), which was shown to affect the elevation of plasma glucose level by oral sugar tolerance test in rats [14]. Hypoglycemic activity-guided fractionation on the rhizomes of *Anemarrhena asphodeloides* yielded steroidal glycosides, pseudoprotoimosaponin AIII, (13) and prototimosaponin AIII, (14). These compounds exhibited hypoglycemic effects in a dose-dependent manner in streptozotocin-diabetic mice but showed no effects on glucose uptake and insulin release, suggesting that the hypoglycemic mechanism may be due to inhibition of hepatic gluconeogenesis and/or glycogenolysis [15].

Charantin (15) a steroidal saponin, obtained from *Momordica charantia* is known to have an insulin-like activity [16]. Charantin stimulates the release of insulin and blocks the formation of glucose in the bloodstream. Similar steroidal saponin (16) was isolated from the fruiting bodies of *Ganoderma applanatum*, which exhibits Rat lens aldose reductase (RLAR) inhibiting activity. The same plant also produced few other class of compounds (65-67) with RLAR inhibiting property [17].

A steroidal saponin, chloragin (17) was isolated from the aerial part of *Chlorophytum nimonii* (Grah) Dalz. The saponin characterized as tigogenin-3-O-α-L-rhamnopyranosyl-(1 → 4)-β-D-glucopyranosyl-(1 → 3)-β-D-xylopyranosyl-(1 →4)-β-D-glucopyranosyl-(1 → 4)-β-D-xylopyranoside showed potent antihyperglycemic activity in streptozotocin induced diabetic rats [18].
Yoshikawa and co-workers isolated elatoside G (18), H (19) and I (20) from a garnish foodstuff "Taranome," the young shoot of Japanese Aralia elata were found to exhibit potent hypoglycemic activity in rats [19]. From Gynostemma pentaphyllum Makino (Cucurbitaceae) a gypenoside saponin, named phanoside (21,23-epoxy-3-β-20,21-trihydroxydammar-24-ene-3-O-[(α-D-rhamnopyranosyl-(1→2))-β-D-glucopyranosyl-(1→3)]-β-D-lyxopyranoside) (21), has been isolated. Phanoside is a dammarane-type saponin and found to stimulate insulin release from isolated rat pancreatic islets. Phanoside (40 and 80 mg/mL) improved glucose tolerance and enhanced plasma insulin levels at hyperglycemia, when given orally to rats [20].

Coagulin C (22), 17β-hydroxywithanolide K (23), withanolide F (24), coagulanolide (25) and coagulin L (26), isolated from the fruits of Withania somnifera, showed significant inhibition on postprandial rise in hyperglycemia post sucrose load in normoglycemic rats and in streptozotocin-induced diabetic rats. Coagulin L (26) showed significant fall in peripheral blood glucose profile and also improved the glucose tolerance of db/db mice [21].

Methanolic extract of the leaves of Boussingaultia baselloides yielded four nor-saponins and a saponin with hypoglycemic activity (27-31). Amongst these, boussingoside A1 (31) exhibited very strong hypoglycemic activity in rats [22].

3.3. Diterpenoids

Diterpenoids are composed of four isoprene units and have the molecular formula C_{20}H_{32}, which are derived from geranylgeranylpyrophosphate pathway. Andrographolide (32), a diterpenoid lactone, obtained from
Andrographis paniculata was found to possess significant hypoglycemic activity [23]. A modified diterpene, saudin (33) was isolated from the leaves of Cluytia richardiana (Euphorbiaceae) growing in Saudi Arabia. It is related to the labdane-type of diterpenes with a novel rearrangement of lactone groups, was found to possess hypoglycemic activity when tested in alloxan induced diabetic rats [24]. Bioassay-guided fractionation of the EtOH extract of Maprounea africana, on noninsulin-dependent diabetes mellitus db/db mouse model, resulted in the isolation of a daphnane-type diterpenoid, maprouneacin (34) which showed potent glucose-lowering properties by the oral route [25].
3.4. Sesquiterpenoids

Sesquiterpenoids consist of three isoprene units and have the molecular formula C_{15}H_{24}. A sesquiterpene lactone, lactucain C (35) and furofuran lignan, lactusaside (77), were isolated from *Lactuca indica* which showed *in vivo* antihyperglycemic activity profile $\Delta -22.74 \pm 12.53\%$ and $\Delta -17.95 \pm 5.63\%$ using STZ-diabetic rats at a dose of 1 $\mu$M/kg [26].

3.5. Alkaloids

An alkaloid is a naturally occurring nitrogenous organic molecule that has a pharmacological effect on humans and other animals. Berberine (36) is known to have potent hypoglycemic activity. It was obtained from the traditional medicinal plant *Tinospora cordifolia* [27]. The mode of its antihyperglycemic activity was investigated in the Caco-2 cell line. Berberine effectively inhibited the activity of disaccharidases in Caco-2 cells, decreased sucrase activity after pre-incubation with Caco-2 cells for 72 h but failed to produce any significant effect on gluconeogenesis and glucose consumption of Caco-2 cells, suggesting that the antihyperglycemic activity of berberine is at least partly due to its ability to inhibit $\alpha$-glucosidase and decrease glucose transport through the intestinal epithelium [28].

Other alkaloids such as catharanthine (37), vindoline (38) and vindolinine (39) obtained from *Catharanthus roseus* also lower blood sugar level [29]. Arecoline (40), an alkaloid isolated from *Areca catechu* was investigated and reported to have hypoglycemic activity in an animal model of diabetes upon subcutaneous administration [30].
Cryptolepine (41) is a rare example of a natural product whose synthesis was reported prior to its isolation from *Cryptolepis sanguinolenta*. Cryptolepine and its salts form lower blood glucose in rodent models of type II diabetes. To optimize this natural product lead, a series of substituted and hetero substituted cryptolepine analogs was synthesized [31].

Aegeline (42), an alkaloidal-amide from the leaves of *Aegle marmelos*, was isolated by our group and was found to have antihyperglycemic activity as depicted from the lowering of the blood glucose levels by 12.9% and 16.9% at 5 and 24 h, respectively, in sucrose challenged streptozotocin induced diabetic rats (STZ-S) model at the dose of 100 mg/kg body weight. The reasonable mapping of compound to a validated pharmacophoric hypothesis and 3D QSAR model with an estimated activity (283 nM) suggested that aegeline might be a β3-adrenergic receptor (AR) agonist [32].

Hypoglycemic activity of trigonelline (43) and 4-hydroxyisoleucine (57) isolated from seeds of *Trigonella foenum graecum* viz was evaluated in alloxan induced diabetic mice. The combination of 4-hydroxyisoleucine and trigonelline [4-HIT, 40: 30, 120 mg/kg] was administered orally in alloxan induced diabetic mice. After 28 days treatment with 4-HIT, there was significant decrease in blood glucose level. 4-HIT increased the glucose threshold as compared to only alloxan treated group. Histology of pancreas showed formation of new islets near the vicinity of the pancreatic duct. Glyburide was used as a standard antidiabetic drug and its effect on pancreatic cell was also studied. The pancreatic β cells of glyburide treated mice did not show any islets in the vicinity of pancreatic duct. LD50 was found to be more than 5000 mg/kg. These results suggested that 4-HIT showed hypoglycemic effect in alloxan induced diabetic mice. The presence of the pancreatic islets in the vicinity of duct suggested that 4-HIT might act by regeneration of new islets [33].

The therapeutic potential of *Galega officinalis* for the management of diabetes was defined in the first half of the twentieth century. *G. officinalis* is a rich source of guanidine and related molecules, which account for its biological effects. The toxicity of guanidine precludes its use clinically, and experiments by Georges Tanret in the years immediately before the Great War identified a less toxic guanidine-like alkaloid, galegine (44) [34]. The synthetic biguanides such as metformin (45) and its analogues were synthesized on the basis galegine chemical structure.

### 3.6. β-Carbolines

The β-carboline alkaloids Harmane (46), norharmane (47) and pinoline (48), were found to increase insulin secretion two to three-fold from isolated
human islets of langerhans. Harmane and norharmane obtained from *Tribulus terrestris* may account for the hypoglycemic property of the plant [35]. Harmane stimulates insulin secretion in a glucose-dependent manner. The results strongly substantiated the claim of β-carbolines as potent insulin secretagogues [36]. Harmine (49) is found in Syrian rue (*Peganum harmala*) and other plants. Recently Waki and co-workers through a small-molecule library screen has identified it as a proadipogenic that acts by inducing PPARγ expression. Obese (db/db) mice treated with harmine show a delay in the onset of diabetes, coincident with increased oxygen consumption and thermogenesis. A 2-fold increase in PPARγ levels was selectively seen in white adipose tissue, while there was a 50% decrease in PPARγ levels in the liver and no change in muscle, brown adipose tissue, or kidney. The effect of harmine on PPARγ expression in the brain and pancreas is currently unknown [37].
3.7. Carbohydrates

Two hypoglycemic principles, ganoderan B (50) and C (51), isolated from the fruit bodies of *Ganoderma lucidum* were shown to be peptidoglycans with mol wts of 7400 and 5800, respectively. Physicochemical and chemical studies demonstrated that the backbone and side chains of ganoderan B contain D-glucopyranosyl $\beta-1\rightarrow3$ and $\beta-1\rightarrow6$-linkages while those of ganoderan C contain D-glucopyranosyl $\beta-1\rightarrow3$ and $\beta-1\rightarrow6$-linkages and a D-galactopyranosyl $\alpha-1\rightarrow6$-linkage [38].

![Chemical structure of ganoderan B and C](image)

3.8. Amino acids

FR225659 (52) and four related compounds (53-56) are gluconeogenesis inhibitors that consisted of an acyl-group and three unusual amino acids. They were isolated from the culture broth of *Helicomyces* sp. and purified by absorptive resin and reverse-phase column chromatography. They were found to be potent inhibitors of gluconeogenesis in primary cultured rat hepatocytes and thus may be useful as anti-diabetic agents [39]. *T. foenum-graecum* (Leguminosae family) is an annual herbaceous plant commonly known as fenugreek and is widely distributed across Asia, Africa, and Europe. Fowden [40] was the first to isolate and identify the unusual amino acid, 4-hydroxyisoleucine (57). Christophe et al. [41] discovered that the major isomer $2S,3R,4S$ of 4-hydroxyisoleucine induces insulin secretion through a direct effect on pancreatic $\beta$ cells in rats and humans. Recent studies by our group also confirm the antihyperglycemic activity [42]. The plant *Blighia sapida* belongs to sapindaceae family, which is known for its poisonous properties. Two unusual amino acids such as hypoglycin A (58) and hypoglycin B (59) isolated from this plant possess antihyperglycemic activity [43].
3.9. Miscellaneous

Salacinol (60) has been isolated from an antidiabetic ayurvedic traditional medicine, *Salacia reticulata*, through bioassay-guided separation and was found to be most potent natural α-glucosidase inhibitor [44].

Allicin (thio-2-propene-1-sulfinic acid S-allyl ester) (61), a sulphur compound isolated from garlic (*Allium sativum*) has resulted in pronounced hypoglycemia in mildly diabetic rabbits upon oral administration (0.25 mg/kg) [45]. S-allyl cysteine sulphoxide (62), a sulphur containing amino acid which is the precursor of allicin and garlic oil, has been found to show significant antidiabetic effects in alloxan diabetic rats at a dose of 200 mg/kg body weight [46]. Leporin B (63), a demethylated analog of leporin A (64) was isolated from a taxonomically unidentified fungal strain to discover compounds with the ability to increase expression levels of the enzyme hexokinase II [47].
Rat lens aldose reductase (RLAR) inhibitors (65-67 and 16) from the fruiting bodies of *Ganoderma applanatum* were isolated, protocatechualdehyde (67) was the most potent RLAR inhibitor (IC$_{50}$ = 0.7 μg/mL) equivalent to that of the positive control TMG (IC$_{50}$ = 0.6 μg/ml) [17].

2-Arylbenzofuran, puerariafuran (68) was isolated from MeOH extract of the roots of *Pueraria lobata* as active constituent, using an *in vitro* bioassay based on the inhibition of advanced glycation end products (AGE). The compound (68) and coumestrol (69) exhibited a superior inhibitory activity against AGEs formation with IC$_{50}$ values of 0.53 and 0.19 μM, respectively, compared to a well known positive control, aminoguanidine (IC$_{50}$ value of 473 μM) [48].

Two compounds *viz*, kodaistatin A (70) and kodaistatin C (71) were isolated from cultures of *Aspergillus terreus*. The kodaistatins are effective inhibitors of the glucose-6-phosphate translocase component of the glucose-6-phosphatase system (EC 3.1-3.9), an enzyme system which is important for the control of blood glucose levels. The IC$_{50}$ was 80 nM for kodaistatin A and 130 nM for kodaistatin C [49].
The glucose lowering effect of mangiferin (72), a xanthone glucoside, isolated from the leaves of *Mangifera indica* was studied in streptozotocin-induced diabetic rats. Hypoglycemic activity of mangiferin (10 and 20 mg/kg, i.p. once daily for 28 days) at different time intervals in STZ induced diabetic rats and improvement in oral glucose tolerance in glucose-loaded normal rats upon chronic administration (10 and 20 mg/kg, i.p.) for 28 days was observed [50].

A xanthone, which is close analogue of mangiferin was isolated from the hexane fraction of the plant, *Swertia chirayita*, identified as 1,8-dihydroxy-3,5-dimethoxyxanthone (swerchirin: 73). It has a very significant blood sugar lowering effect in fasted, fed, glucose loaded, and tolbutamide pretreated albino rat models. The ED$_{50}$ for 40% blood sugar lowering in CF male albino rats (body weight 140-165 g) is 23.1 mg/kg/oral [51].

Various active components like (−)-epicatechin (74), the benzofuranone, marsupsin (75) and the stilbene, pterostilbene (76) isolated from the bark and heartwood of *Pterocarpus marsupium* were evaluated for their putative antihyperglycemic activity against streptozotocin-induced hyperglycemic rats and were found to possess blood sugar lowering activity. The phenolic constituents viz, marsupsin (75) and pterostilbene (76) significantly decreased the plasma glucose level of STZ-induced diabetic rats by -33% and -42% respectively. The antidiabetic activity of pterostilbene (-42%) was comparable to that of the reference compound, metformin (-48%) [52].
A furofuran lignan, lactucaside (77) along lactucain (35) was isolated from *Lactuca indica* which showed *in vivo* antihyperglycemic activity profile Δ -17.95 ± 5.63% using STZ-diabetic rats at a dose of 1 μM/kg [26].

Ferulic acid (78) is polyphenolic compound found in many medicinal plants such as *Curcuma longa*. Ohnishi and co-workers from Japan demonstrated its antihyperglycemic activity in insulin dependent (IDD) and non-insulin dependent diabetes mellitus models (NIDDM) [53]. Similar class of compound that is cinnamaldehyde (79) was isolated from *Cinnamomum zeylanicum* (cinnamon) exhibits potent antihyperglycemic activity in streptozotocin (STZ)-induced male diabetic wistar rats [54]. Both the compounds also possesses hypolipidemic properties [51,52].

### 4. Dyslipidemia

Dyslipidemia is elevation of plasma cholesterol, triglycerides (TGs), or both, or a low high density lipoprotein level that contributes to the development of atherosclerosis. Causes may be primary (genetic) or secondary. Diagnosis is by measuring plasma levels of total cholesterol, TGs, and individual lipoproteins. When carbohydrates are in low supply or their breakdown is incomplete, fats become the preferred source of energy in diabetic patients. As a result, the fatty acids are mobilized into the general circulation leading to secondary triglyceridemia in which total serum lipids in particular triglycerides as well as the levels of cholesterol and phospholipids
increase. This rise is proportional to the severity of the diabetes. Uncontrolled diabetes is manifested by a very high rise in triglycerides and fatty acid levels. An increase in plasma lipids, particularly cholesterol, is a common feature of atherosclerosis, a condition involving arterial damage, which may lead to ischemic heart disease, myocardial infarction, and cerebrovascular accidents. These conditions are responsible for one-third of deaths in industrialized nations [55].

5. Current therapeutics

Current antidyslipidemia drugs include statins, fibrates, niacin, ezetimibe, and bile acid binding resins (Table-2).

These drugs target one component of the lipid profile, with smaller additional effects on other parameters. For instance, statins and fibrates produce sizable reductions primarily in plasma LDL-C and TG, respectively. Meanwhile, niacin has the greatest HDL-C raising capacity. However, many high CHD risk patients fail to reach strict guideline target levels with currently

<table>
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<th>Medication</th>
<th>Effects on lipid parameters</th>
<th>Adverse effects</th>
</tr>
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<tr>
<td>Statins (HMG-CoA reductase inhibitors)</td>
<td>↓ ↓ LDL-C, ↓ TG, Minimal effects on HDL-C (rosuvastatin can increase HDL-C levels)</td>
<td>Myalgias, Myositis/rhabdomyolysis Transaminitis</td>
</tr>
<tr>
<td>Fibrates (PPAR-α agonists)</td>
<td>↓ LDL-C, ↓ ↓ TG, ↑ HDL-C (mild)</td>
<td>Myalgias, Rhabdomyolysis Cholelithiasis, Elevations in serum creatinine</td>
</tr>
<tr>
<td>Ezetimibe (intestinal cholesterol absorption inhibitor)</td>
<td>↓ LDL-C, ↓ TG</td>
<td>Myalgias (very rare) Rhabdomyolysis (very rare)</td>
</tr>
<tr>
<td>Niacin</td>
<td>↓ ↓ TG, ↑ ↑ HDL-C, ↓ ↓ LDL-C, ↓ ↓ LP (a)</td>
<td>Flushing/vasodilation Impair insulin sensitivity Gout, gastric</td>
</tr>
<tr>
<td>Bile acid resins (inhibitors of enterohepatic circulation)</td>
<td>↓ LDL-C</td>
<td>↑ TG Bloating, constipation Interference with absorption of other, medications such as levothyroxine, warfarin, digoxin, statins</td>
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available drugs. A small but clinically relevant proportion of patients experience adverse effects. Thus, additional pharmaceutical strategies are required to fill these gaps in efficacy and tolerability. Plants have always been an exemplary source of drugs and many of the currently available drugs have been derived directly or indirectly from them.

5.1. Sterols and triterpenoids

A number of studies, both in animal models and human clinical trials, have shown that guggulipid (80,81) isolated from the Resin of the gum of the guggul tree, Commiphora mukul, has beneficial effects on serum lipoprotein profiles [56]. A pregnane glycoside roylenine (82) was isolated from Marsdenia roylei. The glycoside (82) and its acetylated derivative showed significant antioxidant and antidyslipidemic activities [57].

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\begin{align*}
\text{80} & & \text{81} & & \text{82} \\
\end{align*}
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A steroidal saponin, chloragin (17) [tigogenin-3-\(O-\alpha\)-L-rhamnopyranosyl-(1 \(\rightarrow\) 4)-\(\beta\)-D-glucopyranosyl-(1 \(\rightarrow\) 3)-\(\beta\)-D-xylopyranosyl-(1 \(\rightarrow\) 4)-\(\beta\)-D-xylopyranoside] was isolated from the aerial part of Chlorophytum nimonii (Grah) which showed potent antidyslipidemic activities in albino rats [18]. Coagulin L (26) isolated from Withania somnifera showed significant fall in peripheral blood glucose profile and also improved the glucose tolerance of db/db mice. It also showed antidyslipidemic activity in db/db mice that is comparable to median effective dose of fenofibrate i.e., 50 mg/kg body weight [21].

Sudhahar and co-workers reported hypercholesterolemia in lupeol (83) and linoleate ester of lupeol (84) [58]. We have also prepared several ester derivatives of lupeol and studied their structure activity relationship. Some of the derivative showed potent activity than the lupeol. Lupeol nicotenate (85) was found to be the most potent triglyceride lowering agent in addition to antihyperglycemic activity [59].
Wiedendiol-A (86) and B (87), sesquiterpene-hydroquinones which inhibit cholesteryl ester transfer protein (CETP), have been isolated from the marine sponge Xestoepongia wiedenmayeri [60].

Statins are currently marketed drugs used to lower the plasma cholesterol levels in humans. Natural statins obtained from different genera and species of filamentous fungi. Lovastatin (88) is mainly produced by Aspergillus terreus strains and mevastatin (89) by Penicillium citrinum. Pravastatin (90) was obtained by the biotransformation of mevastatin by Streptomyces carbophilus and simvastatin (91) by a semi-synthetic process, involving the chemical modification of the lovastatin side chain. The hypocholesterolemic effect of statins lies in the reduction of the very low-density lipoproteins (VLDL) and LDL involved in the translocation of cholesterol, and in the increase in the high-density lipoproteins (HDL), with a subsequent reduction of the LDL- to HDL-cholesterol ratio, the best predictor of atherogenic risk [61].
Several synthetic statins such as atorvastatin (92), cerivastatin (93), pitavastatin (94) and rosuvastatin (95) were developed on the basis of structures of natural statins.

A diterpene, (96) which has close structural features of statins was isolated from the leaves of *Polyalthia longifolia* [62]. This compound showed significant antidyslipidemic activity in high diet (HFD) fed dyslipidemic hamsters at different doses.

5.2. Polyphenolic compounds

Few naturally occurring flavanones and their glycosides such as hesperetin (97), hesperidin (98), naringenin (99), and naringin (100) have been reported as potential agents for improving the cholesterol metabolism in diet-induced hypercholesterolemic animals [63]. We also isolated three modified furano-flavonoids (101-103) and a rare flavonol glycoside (104) as an antidyslipidemic agents from the aerial parts of *Indigofera tinctoria* [64]. Flavonoid mixture (101 and 102) showed potent triglyceride lowering activity in high fat fed hamster model.
Eriocitrin (105) (eriodictyol 7-O-β-rutinoside) is the main flavonoid in lemon fruit (Citrus). Eriocitrin was effective in lowering effect on serum and hepatic lipids in high-fat and high-cholesterol fed rats [65].

Pterosupin (106) and liquiritigenin (107) were isolated from the heartwood of Pterocarpus marsupium showed hypolipidemic activity in Triton model. Both the compounds lowered the serum cholesterol and LDL-cholesterol. Pterosupin also lowered the triglycerides [66].
Rutin (108) is flavonoid glycoside found in many plants and is also an important dietary constituent of food and plant-based beverages. Several studies demonstrated lipid lowering effect of rutin. Recently Amir and co-workers reported its anti-hypercholesterolaemic effect (plasma cholesterol and LDL-C) in rat model [67]. Odbayar and co-workers from Japan studied the effect of quercetin (109) and its glycoside (rutin) and their studies indicated that quercetin better than the rutin in reduction of hepatic lipogenesis (hypolipidemic effect) [68].

Tso-Hsiao Chen and co-workers studied about 40 flavonoids for their HMG-Co-Enzyme reductase activity. Astilbin (110) was the only effective HMG-Co-Enzyme reducates inhibitor in their studies, which demonstrates its hypocholestereamic activity [69].

Kurarinol (111) is a prenylated flavanone, which is known for its alpha glucosidase, beta amylase and diacylglyceral transferase activity. Kuraridinol (112) is a prenylated chalcone. Both were isolated from the Sophora flavescens showed significant hyperlipidemic and hypercholesterolemic effect. Kuraridinol was more potent than kurarinol in their studies [70].
Resveratrol (113), a naturally occurring stilbenoid commonly available in red wine act as a free-radical trap to halt the progression of LDL oxidation. It is very strong antioxidant and mild lipid lowering agent, which certain extent prevents the development of atherosclerosis [71]. Resveratrol derivatives such as, pterostelbene (76) and trimethylated resveratrol (114) and its analogue Piceatannol (115) have been studied for their PPAR alpha activity and in-vivo hyperlipidemic activity. Pterostelbene showed good PPAR alpha agonist activity and hypolipidemic activity than other compounds [72]. Polydatin (116) is glycoside of resveratrol isolated from Polygonum cuspidatum also has been reported for its lipid lowering effect in high fat diet fed hamster [73].

Mangiferin (72) a xanthone glucoside, isolated from the leaves of Mangifera indica showed significant antihyperlipidemic activity at a dose of 10 and 20 mg/kg, i.p. Further, in streptozotocin-induced diabetic rats it showed antiatherogenic activities as evidenced by significant decrease in plasma total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C) levels coupled together with elevation of high density lipoprotein cholesterol (HDL-C) level and diminution of atherogenic index in diabetic rats [50].
Bergenin (117) is commonly available in many plants of Euphorbiaceae, Saxifragaceae and Myrsinaceae. It is a $C$-glucoside of 4-$O$-methylgallic acid. Oral administration of bergenin isolated from the leaves of *Flueggea microcarpa* reduced the serum cholesterol, triglycerides, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL)-cholesterol levels were significantly [74].

5.3. Alkaloids

Berberine (36), a natural plant alkaloid isolated from the root of *Berberis oblonga*. *In vitro* and *in vivo* studies have showed its effects on hyperglycemia and dyslipidemia [75].

Our activity guided fraction and isolation work o the leaves of *A. marmelos* led to isolate an alkaloidal-amide, Aegeline (42) and found to have antihyperglycemic activity as well as hypolipidemic activity [32]. Aegeline has strong triglyceride lowering activity in our studies and the activity was comparable with the marketed drug i.e. fenofibrate. Hsu and coworkers showed that arecoline (40) inhibited adipogenesis as determined
by oil droplet formation and adipogenic marker gene expression. There further studies indicated that arecoline induced lipolysis in an adenylyl cyclase-dependent manner [30].

5.4. Amino acid

We isolated an unusual amino acid 4-hydroxyisoleucine (57) from the seeds of *T. foenumgraecum*, which significantly decreased the plasma triglyceride levels by 33% (P < 0.002), total cholesterol (TC) by 22% (P < 0.02), and free fatty acids by 14%, accompanied by an increase in HDL–C/TC ratio by 39% in the dyslipidemic hamster model [11]. 4-Hydroxyisoleucine is also very good insulin releasing agent.

5.5. Miscellaneous

C₆₀-polyprenol (118) was isolated from the chloroform fraction of the ethanol extract of *Coccinia grandis*. It significantly decreased serum TG by 42%, total cholesterol (TC) 25% and glycerol (Gly) 12% and increased HDL-C/TC ratio by 26% in high fat diet (HFD)-fed dyslipidemic hamsters at the dose of 50 mg/kg body weight as compared to the standard drug fenofibrate at the dose of 108 mg/kg [76].

S-methyl cysteine sulfoxide –SMCS (119) isolated from *Allium cepa* was investigated for its lipid lowering action in SD rats. SMCS at a dose of 200 mg/kg body weight for 45 days enhanced the hyperlipidemic condition. Concentrations of cholesterol, triglyceride and phospholipids were significantly reduced with respect to control [77]. Itokawa and co-workers also reported the lipid lowering activity in S-methyl cysteine sulfoxide (SMCS) and S-allylcysteine sulfoxide (62) [78].

Ferulic acid (78) and cinnamaldehydes (79) which are commonly available in many medicinal plants have been reported for their lipid lowering activity as well as anthyperglycemic activity [51,52].
6. Conclusion

Type-II diabetes poses a lethal threat to mankind in the present health scenario. The more alarming situation has raised owing to the secondary complications such as atherosclerosis, (ischemic heart disease, myocardial infarction, and cerebrovascular accidents) associated with this silent killer. So, there is an urgent need for broad based drugs which can ameliorate this complex menace. Natural products have always been the inexhaustible source of new drugs from the time immemorial. Notwithstanding the significant headways in synthetic chemistry in the management of hyperglycemia and hyperlipidemia, chemical entities emanating from the natural source still hold promise in alleviating the blood glucose levels and lipids and its concurrent ailments. More has been done but much has remained unexplored in the drug discovery paradigm of natural products attributed with therapeutic virtues. Some targets have been identified for the active principles but unless, their mechanism of action is not determined and clinical studies not performed, their potential as antihyperglycemics and antidyslipidemics will remain unearthed. Moreover, the combination of plant based drugs and synthetic pharmaceuticals for correcting this metabolic error could pave way for cost-effective therapies. The scope of plant drugs lies in the rectifying the problem of adverse side effects generated by synthetic drugs, cost-effectiveness and minimal side-effects. The resurgence of natural products in the drug discovery and development may hold the key in the proper utilization of biodiversity for the management of hyperglycemia and hyperlipidemia.

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References


Naturally occurring antihyperglycemic and antidyslipidemic agents


