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Analysis of phytoconstituents of medicinal plants for the treatment (management) of type 2 diabetes mellitus (T2DM): A review

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Abstract
Gradual development of hyperglycemia, hyperlipideamea, insulin resistance, beta cell dysfunction, defects in GLUT4 translocation and insulin signaling receptors etc. lead to the development of type 2 diabetes mellitus, T2DM. The parallel research focuses on glucose homeostasis is gluconeogenesis/glycogenesis, absorption of glucose by gut and re-absorption of glucose by kidney etc. Different medicinal plants have different phyto-molecules which can be used for the treatment of the above said defects/metabolic syndromes. The effect of some phyto-molecules used for the treatment of T2DM can be compared with the already existing drugs and the phyto-molecules may not have side effects. Extraction and use of suitable phyto-molecules in the form of crude drugs for the treatment of the above said defects/metabolic syndromes are now on the research focus and this review analyzes the various phyto-molecules involved in the treatment of these different defects/metabolic syndromes of T2DM. Formulation of crude drug containing effective phyto-molecules from poly-herbs to activate different pathways, to treat the metabolic syndromes and to increase the health of the islet cells is the need of the hour.

Keywords: metabolic syndromes, Poly-herbal, crude drug, phyto-molecules

1. Introduction
Among life style disorders, highly prevalent in India [1] and worldwide [2] with high projection of its prevalence is type 2 diabetes mellitus. The high growth rate of T2DM in India and worldwide is the indication of the worldwide change of life style and nutrition [3, 4]. T2DM develops from the age of 15 years as reported earlier [5, 6] and its cumulative effect is the development of *metabolic syndromes*, hyperglycemia, hyperlipideamea, insulin resistance etc., *diabetic complications*, nephropathy, neuropathy, diabetic encephalopathy and cardiovascular diseases etc. and *early mortality*. Some important treatment measures focused are to increase the effectiveness of the pancreas by making efforts to reduce β-cell early mortality [7] and increasing secretion and sensitivity of the insulin, to regulate synthesis and absorption of glucose during anomalous plasma glucose level, to stabilize the activators of the GLP-1 (glucagon-like peptide-1 receptor), to inhibit DPP-4, an enzyme which destroys GLP-1 [8-10] etc. and may be in the near future, efforts to protect receptors involved in glucose homeostasis against mutation. The most important events in glucose homeostasis is insulin stimulated glucose transport by glucose transporters and among the glucose transporters, GLUT4 plays a very important role in transporting glucose to muscles [11, 12]. Specifically, entry of glucose in to the cells needs translocation of GLUT 4 and other transporters such that both insulin and exercise stimulate translocation of GLUT 4 [13, 14]. Moreover, insulin secretion and release by β-cells is stimulated by glucose, free fatty acids, neurotransmitter such as acetylcholine, certain amino acids such as leucine [15] etc. and many of these and other very active phyto-molecules for this purpose are extracted from the medicinal plants using single plant or many plants together. Apart from the available drugs on the focused areas of the treatment, this article highlights the need of phyto-molecules in place or in addition to the available drugs for the effective treatment measures of T2DM. Although there are reviews analyzing importance of phyto-molecules [16], this may be an another highlight.

2. Plant crude drug extracts (Phyto-constituents)
Extract of medicinal plants can be obtained from any part of the plant using suitable solvents, petroleum ether, chloroform, benzene, ethanol, methanol, water etc., an extraction process, maceration, percolation, soxhelet extraction method, Supercritical fluid extraction method [17] etc. Soluble plant crude drug extract (either in single solvent or combination of solvents) obtained from the respective plants is used for testing in animals and latter in humans against a

particular disorder [18]. Since crude drug extracts are specific phyto-constituents of the medicinal plants (mostly due to the dissolution of particular phyto-constituent in a suitable solvent) [19], their activity and effect may produce achievable output after the treatment with either in animals or humans without producing much of the side effect. Table 1 shows few medicinal plants, their nature of solvent extracts and their effect on T2DM. Table 2 shows the isolated phyto-molecules from the respective plants and their usage to reduce the effect of specific metabolic syndromes.

Table 1: Medicinal plants having anti-diabetic effect

S. No.	Name of the Plant	Family	Phytoconstituents / Form of crude drug	Effect on T2DM	Ref.
1.	*Achyranthes aspera*	Amaranthaceae	Aqueous extract & alcoholic extract Methanolic extract	Improves blood pressure &hypertension Hypolipidemic Improves aminotransferases against rifampicin induced liver toxicity.	[76] [56] [74]
2	*Azadirachta indica*	Meliaceae	Chloroform extract	Anti-diabetes and anti-oxidative stress	[55]
3.	*Adhatoda vasica*	Acanthaceae	Extract Plant powder	Anti-oxidant & improves encephalopathy Hepatoprotective	[37] [68]
4.	*Aloe vera*	Liliaceae	Gel extract	Beneficial effect on lipid profile. Antioxidant Reduce visceral fat accumulation	[87, 29] [30] [57]
5.	*Berberis lycium*	Berberidaceae	Alcoholic extract Root bark extract Crude powder Crude powder	Hepatoprotective Improves lipid profile Stimulates glucose transport Reduces Cholesterol Hepatoprotective	[86] [32] [33] [60]
6.	*Brassica olearancea*	Brassicaceae	Hydro-soluble extract	Anti-hyperlipidemia	[58]
7.	*Curcuma longa*	Zingiberaceae	Extract	Reduces Cholesterol	[62]
8.	*Coriander sativum*	Umbelliferae	Extract	Reduces Cholesterol	[61]
9.	*Cassia auriculata*	*Fabaceae*	Flower extract	Antihyperlipidaemic & antidiabetic	[31]
10.	*Emblica officinalis*	Phyllanthaceae	Methanolic extract Methanolic extract	Inhibits Aldose reductase Inhibits α-amylase and α-glucosidase Reduce lipid profile Hepatoprotective from antituberculosis drug	[38] [63] [64] [75]
11.	Ferula asafoetida	Umbelliferae	Petroleum ether, chloroform, benzene, ethanol and water extracts	Hepatoprotective against carbon tetrachloride liver toxicity Improves blood pressure	[85] [77]
12.	*Gallium asparine*	Rubiaceae	Crude powder	Hepatoprotective	[86]
13.	*Momordica charantia*	Cucurbitaceae	Alcoholic extract Petroleum ether, chloroform, benzene, ethanol and water extract	Antidiabetic. Prevents polyuria and polydepsia Suppress gluconeogenic enzymes Anti-hyperlipidemia Hepatoprotective against carbon tetrachloride liver toxicity	[40] [44] [45] [66]
14.	*Nordostachys jatamansi*	Caprifoliaceae	Alcohol extract	Hepatoprotective	[85]
15.	*Piper nigrum*	Piperaceae	Extract	Hepatoprotective Reduce blood pressure Act as vasomodulator	[71] [79] [78]
16.	*Pistacia integerrima*	Liliaceae	Crude powder	Hepatoprotective	[86]
17	*Pongamia pinnata*	Leguminoseae	Extract	GLUT4 translocation	[50]
18.	*Rhododendron arboreum*	Ericaceae	Methanolic flower extract Ethyl acetate extract	Inhibits α-glucosidase Hepatoprotective against carbon tetrachloride liver toxicity	[36] [70]
19.	*Terminalia bellerica*	Combretaceae	Extract	LDL oxidation	[63]
20.	*Trigonella foenum*	Fabaceae	Extract	GLUT4 translocation	[51]
21	*Hippophae rhamnoides*	Elaeagnaceae	Leaf extract	GLUT4 translocation	[53]

Table 2: Main phyto-compound of medicinal plants and their effects on T2DM

S. No	Name of Phytocompounds	Plant Name	Effect on T2DM	Ref
1	Chitosan	*Aloe vera & Brassica olearacea*	Hypolipidemic activity	[58]
2	Curcumin	*Curcuma longa*	Reduce uptake of cholesterol from gut	[62]
3	Lophenol & Cycloartanol	*Aloe vera*	Reduces visceral fat accumulation	[57]
4	Ellagic acid and Ascorbic acid	*Emblica officinalis*	Antidiabetic activity	[63]
5	Achyranthine	*Achyranthes aspera*	Reduce hypertension	[76]
6	Piperine	*Piper nigrum*	Act as vasomodulator	[78]
7	Berberine	*Berberis lycium*	Antidiabetic activity	[34]
8	Laligurans	*Rhododendron arboretum*	Antidiabetic activity	[36]

9	Charantin,	*Momordica charantia*	Glucose tolerance	[40]
10	P-insulin	*Momordica charantia*	Function like insulin	[41]
11	lectin	*Momordica charantia*	Antidiabetic activity	[42, 43]
12	Momordicin	*Momordica charantia*	Primary anti-diabetic active component	[46, 47]
13	Pongamol and karanjin	*Pongamia pinnata*	Stimulate GLUT4 translocation	[50]
14	4-hydroxyisoleucine	*Trigonella foenum*	Stimulate GLUT4 translocation	[51]
15	Transina	formulation of *Withania somnifera*, *Tinospora cordifolia*, *Eclipta alba*, *Ocimum sanctum* and *Picrorrhiza kurroa*	Decrease hyperglycaemia due to the pancreatic islet free radical scavenging activity	[84]
16	Gallic acid	*Hippophae rhamnoides*	Stimulate GLUT4 translocation	[52]
17	Lophenol, 24-methyl-lophenol, 24-ethyl-lophenol, cycloartanol, and 24-methylene-cycloartanol	*Aloe vera*	Long term glucose control	[87]

3. Analysis of Phyto-constituents

The phyto-constituents of five medicinal plants have been reviewed, *Momordica charantia* [20], *Achyranthes aspera* [21], *Aloe vera* [22], *Emblica offinalis* [23] and *Adhatoda vasia* [24] and it is found that all five medicinal plants have different types of amino acids, vitamins, mineral elements, enzymes, carbohydrates, secondary metabolites and unique compounds of their own. The few common compounds found with software are listed below, table 3. Moreover, it is also analyzed that some medicinal plants have rich amino acids, others rich vitamins or minerals etc. and therefore, it has come to a common understanding that phyto-constituents of each plant or group of plants when administrated helps in opening up different pathways for glucose homeostasis and allied sub pathways of the same than a single drug molecule and may have important role in the treatment of T2DM.

Table 3 Analysis of common phyto-molecules among M. charantia, A. aspera, A. vera, E. officinalis, A. vasica

	Momordica charantia	***Achyranthes aspera***	***Aloe vera***	***Emblica officinalis***	***Adhatoda vasica***
Momordica charantia	*	Oleanolic acid	Nil	Zeatin	Nil
Achyranthes aspera	Nil	*	β-sitosterol	β-sitosterol	Nil
Aloe vera	Nil	NIl	*	β-sitosterol	quercetin
Emblica officinalis	Nil	Nil	Nil	*	Nil
Adhatoda vasica	Nil	Nil	Nil	Nil	*

Among the common phyto-molecules from the table 3, Zeatin is a growth hormone, oleanolic acid has antihyperlipidemic properties, β-sitosterol is used to prevent many disorders, heart disease, hypercholesterolemia, modulating the immune system, prevention of cancer etc. [25, 26] and quercetin has been reported to play a role in reducing cardiovascular diseases and anti-inflammation. During an *in vitro* study on isolated rat arteries, quercetin has been demonstrated to be a vasodilator [27]. Combining the above information and the data of tables 1 and 3, it may be concluded that *Memordica charantia* (S. No 13) and *Achyranthes aspera* (S. No 1) are antihyperlipidemic due the presence of oleanolic acid. Similarly, hypercholesterolemia can be treated using *Aloe vera*, *Achyranthes aspera* and *Emblica officinalis* due to the presence of β-sitosterol and the search can continue in this way.

4. Analysis using crude drugs

a) Effect of crude drug on blood glucose level

There are evidences and examples of treatment of T2DM using phyto-constituents of medicinal plants [28]. Normal fasting plasma glucose level and lipid profile [29] and even reduced glycosylated hemoglobin have been achieved after oral administration of *Aloe vera* gel extract to streptozotocin-induced diabetic rats because of *Aloe vera*'s antioxidant effect; according to the study, it is like the existing drug, glibenclamide [30]. Comparable to glibenclamide, antihyperlipidaemic effect in addition to antidiabetic activity have been shown after administering the flower extract of *Cassia auriculata* [31] to the same experimental rats however, the same effect is observed in an experiment on rabbits using root bark extract of *Berberis lycium* (effect on reducing plasma lipid profile) [32]. Although stimulation of glucose utilization due to presence of hydrolysable tannin [33] is observed in many plant extract containing tannic acid, a phyto-molecule berberine, a tetra quinoline isoalkaloid in the extract of *Berberis lycium* [34] shows antidibetic activity along with extra-pancreatic mechanism of action [35] on the secretion of insulin. Flower extract of *Rhododendron arboretum* (Laligurans, commonly called in Nepal) shows inhibitory activity on α-glucosidase, an enzyme which converts polysaccharides to glucose of rat intestine showing antidiabetic potential [36] in preventing the rise of plasma glucose; like the drugs alpha-glucosidase inhibitors. Anti-oxidant and anti-diabetic effect of *Adhatoda vasica* extract on diabetic encephalopathy [37], the inhibitory effect on Aldose reductase enzyme involved in complications of diabetes cataract [38] by the same plant extract and antidiabetic effect of tannoids in delaying cataract on alloxan induced diabetic rats [39] by *Emblica officinalis* extract are additional treatment measures of T2DM by phyto-constituents.

Momordica charantia is very useful in treatment of diabetes because of Charantin, a natural steroidal glycoside from the plant which has same effect as tolbutamide [40] and P-insulin, a polypeptide-P [41] like human insulin which has many effect such as increased glucose uptake and glycogen synthesis, improving insulin release and repair or promote new growth of insulin-secreting β-cells [42] etc. A study advocates the use of dried *Momordica charantia* powder in the diet at 10% level in the meal and this may have positive effect in improvement of fasting plasma glucose and controlling diabetes and its complications [43]. Moreover, *Momordica charantia* has additional effect in preventing polyuria (abnormal dilute unrination) and polydepsia (abnormally great thirst) conditions developed in diabetes [44] and its extract facilitate slow absorption of glucose along the gastrointestinal tract due to the suppression of gluconeogenic enzymes, glucose-6-phosphatase and fructose-1,6-bisphosphatase and an accelerated glucose metabolism through glucose-6-phosphate dehydrogenase [45]. The plant has momordicin, an alkaloid

which is responsible for the bitter taste of the fruit and its extract improves insulin resistance and alters hepatic glucose production [46, 47]. Its hypoglycaemic mode of action is widely considered to be due to AMP-activated protein kinase activity, which is a major cellular regulator of lipid and glucose metabolism [48] and it also has a significant vascular protective effects against vascular complications [49]. GLUT4 translocation is very important event in glucose uptake and natural compounds such as pongamol and karanjin from *Pongamia pinnata* [50] and 4-hydroxyisoleucine from *Trigonella foenum*-graecum [51] have been found to stimulate GLUT4 translocation leading to increased glucose uptake in muscles. Gallic acid is found to stimulate GLUT4 translocation [52] and *Hippophae rhamnoides* shows antioxidant and hepatoprotective properties [53] and translocation of GLUT 4 due the presence of gallic acid in its leaf extract [54]. Extract of many Indian medicinal plants have shown hypoglycemic effect and reduction in oxidative [55] stress.

b) Effect of crude drug on lipid

Extract of *Achyranthes aspera* reduces lipid profile in triton induced hyperlipidemic rats because the extract slows down the absorption of cholesterol [56]. The phytosterols, lophenol and cycloartanol of *Aloe vera* gel have reduced the serum free fatty acid and triglyceride levels and this observation shows that *Aloe vera*-derived phytosterols can reduce visceral fat accumulation [57] thus, reducing obesity. A common compound, chitosan of *Aloe vera* and *Brassica olearacea* extracts has showed best for reducing lipid profile and contribute to the prevention of atherosclerosis [58], an artery plaque due to LDL cholesterol deposition. Life-long intake of *Aloe vera* extract gives superior anti-oxidative effect, gives lifelong protection against free radical-induced oxidative damage of cell organelles and DNA and protects from age-related increase in hepatic cholesterol [59]. Crude powder of *Berberis lycium* root has anti-hyperlipidemic, effect specifically to reduce plasma cholesterol, a study on broilers [60]. Among spices, extract of *Coriandrum sativum* seeds [61] and extract of *Curcuma longa* containing curcumin have been reported to reduce plasma cholesterol level in rats [62]. Extract of *Emblica officinalis* and *Terminalia bellerica* is used in the treatment of diabetes and LDL oxidation and can act as inhibitor of α-amylase and α-glucosidase and its antidiabetic activity is due to the presence of ellagic acid and ascorbic acid in the extract [63]. It has also produced significant protection against high blood pressure and hyperlipidemic effect as comparable with simvastatin (3-hydroxy-3-methylglutaryl-coenzyme-A reductase inhibitor) drug [64] and is very effective against dyslipideamea and oxidative stress while aging [65]. *Momordica charantia* extract was given to diabetic rats having elevated total cholesterol, triglycerides, and phospholipids, decreased HDL and after treatment normalization was achieved [66, 67] in all the components of lipid profile.

c) Hepatoprotective effect of crude drug of medicinal plants

Whole plant crude drug of *Adhatoda vasica* is used against liver disorders: it has equivalent effect as Silymarin drug and has also been found to have better hepatoprotective action against carbon-tetra chloride induced liver damage in rats [68]. Thus, it can be advocated as a potent liver tonic for humans, a study of ethyle acetate extract of *Adhatoda visica* for hepataoprotective effect of the medicinal plant on rats [69]. The substantially elevated serum enzymatic activities of glutamic oxaloacetic transaminase (SGOT), glutamate pyruvate transaminase (SGPT), alkaline phosphatase (SALP), γ-glutamyltransferase (γ-GT) and bilirubin due to carbon tetrachloride induced liver damage was restored to normal by the flower extract of *Rhododendron arboretum* after the estimation of the same along with the activities of glutathione S-transferase (GST), glutathione reductase, hepatic malondialdehyde formation, and glutathione content [70]. *Piper nigrum* also has hepatoprotective [71] effect against liver injury [72]. Administration of extract of *Emblica officinalis* has showed hepatopretective effect in rats by inhibiting hepatic HMG (3-hydroxy-3-methyl-glutaryl) CoA reductase activity and has increased effect of Lecithincholesterol acyltransferase (LCAT) level, both these help the degradation and elimination of cholesterol [73], a study by using *Emblica officinalis* and *Mangifera indica*.

d) Hepato-protective effect of crude drugs against heapto-toxicity induced by existing drugs

Extract of leaves of *Achyranthes aspera* improves aminotransferases such as serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase of the rifampicin induced hepatotoxic liver of albino rats, which is an example of the hepatoprotective effect of crude drug against liver toxicity [74]. Hepatoprotective effect of *Emblica officinalis* has been reported to be used against liver injury caused by antituberculosis drug and this shows that it has antioxidative and membrane stabilizing properties [75] etc.

e) Effect of crude drug on blood pressure and hypertension

As early as in seventies, it was reported the effect of water-soluble extract, Achyranthine of *Achyranthes aspera* for the treatment of hypertension such that the extract had the effect to decrease blood pressure, to dilate blood vessels and additionally had spasmogenic effect [76]. The aqueous extract of *Ferula asafoetida* when administered to anaesthetized rats has resulted with reduction in mean arterial blood pressure [77]. Piperine of *Piper nigrum* is found to be effective in reducing blood pressure of arteries and act as vasomodulator [78] reducing hypertension [79].

f) Effect of crude drug on pancreas

The hypoglycaemic effect of *Aloe vera* plant extract indicates the activation of β-cells showing an insulinogenic effect of the gel extract. The *Aloe vera* gel extract stimulates insulin secretion from the remnant β-cells of the damaged or from regenerated pancreatic β-cells [80]. *Momordica charantia* has significant repairing effect on beta cells to stimulate insulin secretion [81] Antidiabetic activity of aqueous extract of *Ferula assafoetida* against damaged pancreatic β-cells in alloxan-induced diabetic rats [82] is observed with a significant reduction in plasma glucose level and an increase in serum insulin level, a significant rise in insulin secretion by increased β-cells mass in the diabetic rats [83].

g) Effect of Poly-herbal extract in treatment of T2DM

Streptozocin induced hyperglycaemic rats have been treated with Transina (an ayurvedic herbal formulation comprising of *Withania somnifera*, *Tinospora cordifolia*, *Eclipta alba*, *Ocimum sanctum* and *Picrorrhiza kurroa*) to decrease hyperglycaemia. The anti-hyperglycaemic effect may be due to the pancreatic islet free radical scavenging activity [84]. Polyherbal extract of *Ferula asafoetida*, *Momordica*

charantia and Nardostachys jatamansi has been found very active against carbon tetrachloride-induced liver toxicity in wistar rats, found with reduced levels of serum liver enzymes [85]. *Berberis lycium* in combination with *Galium aparine* and *Pistacia integerrima* shows excellent hepato-protective effects and can be concluded that the plants have more curative effect than preventive effect [86].

Five phytosterols, lophenol, 24-methyl-lophenol, 24-ethyl-lophenol, cycloartanol, and 24-methylene-cycloartanol are evaluated for their anti-hyperglycemic effects in T2DM mice from *Aloe vera* gel and it shows a long-term plasma glucose control effect in the treatment of T2DM [87].

5. Summary

The management/treatment of T2DM depends on the involvement of effective signaling molecules for the activation of different pathways starting from insulin secretion to the glucose homoeostasis to achieve the normal plasma glucose and lipid levels. From the review, it is found that all the reviewed plants are antidiabetic with different dimension, many of them normalize plasma glucose level and lipid profile, few are involved in reducing blood pressure and hypertension and more are for the hepato-protective and increase activity of pancreas. Some phyto-molecules are identified for the inhibition of enzymes which may otherwise lead to hyperglycemia and the action of phyto-molecules is compared with available drugs however, if both have equivalently comparable effect, preference goes to phyto-molecules to avoid side effects of drugs. As per the review, crude drug/phytomolecule increases insulin secretion and sensitivity, helps in translocation of GLUT 4 for glucose uptake by muscle cells, induces slow absorption of glucose by gut, makes slow conversion of polysaccharide to glucose, repairs and promote new growth of beta cells (comparable to islet transplantation), reduces visceral fat accumulation and prevents obesity, has antioxidant property which is very important against reactive oxygen species (ROS) which complicates T2DM, prevents atherosclerosis etc. It is also observed the use of poly-herbal phyto-molecules and use of five phyto-molecules of the same plant for the treatment of diabetes.

6. Conclusion

The crude drug obtained from medicinal plants have many active phyto-constituents suitable for the treatment of T2DM by treating metabolic syndromes and activating different pathways required for the glucose homeostasis and therefore, a ply-herbal phyto-molecular formulation is recommended and can be used for the treatment/management of T2DM.

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9. References

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