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DIFFERENT APPROACHES FOR TREATMENT OF TYPE 2 DIABETES MELLITUS WITH SPECIAL REFERENCE TO TRADITIONAL MEDICINES: A REVIEW

Neeraj Verma [a*], Anil Pratap Singh [c], G. Amresh [a], P. K. Sahu [b]

Affiliated to:

[a] Goel Institute of Pharmacy & Sciences, Faizabad Road [Near Indira Canal] Lucknow227105, Uttar Pradesh, India
[b] School of Pharmaceutical Sciences, Siksha 'O' Anusandhan University, Kalinga Nagar, Ghatikia, Bhubaneswar 751003, Orissa, India
[c] Pharmacognosy and Ethnopharmacology Division, National Botanical Research Institute Council of Scientific and Industrial Research], Rana Pratap Marg, P.O. Box No. 436, Lucknow 226001, Uttar Pradesh, India

ABSTRACT

Diabetes mellitus is a global disease found in all nations of the world. Various attempts have been made in search of suitable formulation for diabetes mellitus. Although allopathic treatment helps to control the disease to an extent but regular medication and constant medical supervision some time leads to non patient compliance and compels them to look for alternative measures. Herbal treatment seems to be promising, as scientific analysis of several plants reveal that they posses enormous therapeutic capabilities that modern medicines is searching for. Moreover, due to affordability especially in developing countries where resources are meager and where the coverage by health service is limited, more researchers are now working in this direction. This paper provides a general account of different managements with main focus on scope of herbal drugs and a comprehensive analysis of plants that may provide insights for future study and development of herbal drugs in modern scientific perspective.

Keywords: Diabetes, Drug Management, Deitary Management, Physicial Activity, Antidiabetic Plants

*Corresponding author:
Email: neerajcology@gmail.com

1.0 INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia arising as a result of a relative or absolute deficiency of Insulin secretion, resistance to insulin action, or both. Diabetes is an ailment in which the body does not produce or properly use insulin. Insulin is a regulatory hormone required for energy management. The cause of diabetes continues to be anonymity, although both genetics and environmental factors such as obesity and lack of exercise appear to play roles. Diabetes mellitus is a major and growing public health problem throughout the world, with an expected to 220 million people by 2010. [1] Approximately 10% of patients have type 1 diabetes mellitus (DM), and the remainder have type 2 DM.[2] Recent estimates project that the number of patients diagnosed with Type II diabetes will more than double to 300 million before 2025. Once found in primarily in middle-aged adults hence the terminology "adult onset" diabetes, the disease is now being observed with increasing frequency in young children and adolescents. This group of patients has been reported to suffer from an increased risk of cardiovascular disease, similar to that observed in adults.

Regardless of the type of diabetes, patients are required to control their blood glucose levels with medications and/or by adhering to an exercise program and a dietary plan. Insulin therapy by injection is given to those with type 1 DM and to some patients with type 2 DM. Patients with type 2 DM are usually placed on a restricted diet and are instructed to exercise, the purpose of which primarily is weight control. If diet and exercise fail to lower and stabilize blood glucose levels, oral antidiabetic medication is prescribed. In some cases, insulin injections are necessary. These treatments are associated with adverse effects, and some may produce toxic effects (e.g., thiazolidinediones may cause liver toxicity).[3] Blood glucose monitoring is an essential task for patients suffering from diabetes; thus, any change caused by herbal products to blood glucose levels may alter the amount of medication needed to control blood glucose. Medical science cannot claim that it knows all that needs to be known about this disease, including its management. This is the main reason for the persistent interest all over the world to explore alternative remedies from the so-called "alternative systems" of medicine. This paper reviews the alternative therapies adopted by people with main focus on history, scientific evidence, scope and future of herbal drugs in the management of diabetes.

2.0 DRUG MANAGEMENT OF DIABETES

2.1 Insulin secretagogues

Sulfonylureas glibenclamide, gliclazide, glipizide, glimepiride

Sulfonylureas stimulate the production and release of insulin by binding to a receptor site on the membrane of the pancreatic beta cell. Binding blocks the opening of ATP-dependent potassium channels, which leads to a depolarization of the membrane, leading to an influx of calcium. These events result in an increased production of insulin by the beta cell. The evolution of the third-generation agent glipizide and glyburide was a major advance over the older sulfonylureas.[4]

They are 20-50 times more potent than previous sulfonylureas on a milligram basis. They have a longer biological action than all preceding agents except for chlorpropamide, with a much lower incidence of adverse reactions, such as hyponatremia and reactions to alcoholic beverages. They have low protein binding, so that they have fewer drug interactions. Glimepiride Amaryl was developed more recently and differs from glyburide in several ways.[5] It is more potent, but behaves more like glipizide than glyburide with a good postprandial insulin response and a lower incidence of hypoglycemia than glyburide. A single daily dose of 8 mg is maximal, with very little added benefit from twice-daily administration of this dose level. The major side effect of the sulfonylureas is hypoglycemia. Hypoglycemia is usually associated with reduced oral intake or prolonged exercise, and is more common with longer-acting sulfonylureas than with short-acting agents, such as tolbutamide.

The newer meglitinides, although not chemically sulfonylureas, increase insulin production by a similar mechanism, at the ATP-dependent potassium channels. They are much shorter-acting. Typically taken at the beginning of a meal, they induce an insulin surge, which fades rapidly, thus reducing the risk of later hypoglycemia. Repaglinide was the first such agent introduced.[6] Recently, nateglinide, a D-phenylalanine derivative that appears to be even shorter-acting, has been introduced. There is no added insulin release with these agents over a maximal dose of sulfonylurea. There is a potential advantage in using these agents in situations in which hypoglycemia may have significant risk, such as the elderly and renal and coronary disease patients. The short action of these agents reduces the risk of hypoglycemia, although not entirely eliminating it. The disadvantage of use of these agents is the need for multiple daily doses.

2.2 Insulin sensitisers

2.2.1 Biguanides (metformin)

Metformin is a biguanide that has been marketed in Europe for 30 years. It reduces hepatic glucose production and increases peripheral glucose utilization. The mechanism of action is still poorly understood.[7] The degree of glucose lowering induced by metformin in non-insulin-dependent patients is similar to that of glyburide.[8] Furthermore, when added to glyburide treatment, metformin produced a further substantial reduction in glucose levels.[9] Additionally, it decreases the release of free fatty

acids from adipose tissue and lowers the cholesterol and triglyceride levels.

The most serious complication of biguanide use is lactic acidosis, which can be fatal. Fortunately, the incidence of lactic acidosis with metformin use is low (1 case per 33,000 patient-years) [10]. The risk of lactic acidosis is increased in patients with renal disease. A serum creatinine of 1.5 mg/dL is the suggested upper limit on use of this agent. The risk of lactic acidosis is also increased with dehydration and with the use of radiologic contrast dye. Metformin should be stopped at the time of the radiographic contrast procedure and not restarted for 48 hours. Although lactic acidosis is very rare, a much more common problem with metformin is a high incidence of gastrointestinal complaints. One out of 3 patients will experience problems ranging from mild heartburn to significant diarrhea. Patients do tend to become more tolerant of metformin with time, so that, in some cases, one can reduce the dose and achieve a lower level of gastrointestinal distress. Metformin is contraindicated in congestive heart failure and is relatively contraindicated in the elderly. Unlike insulin and sulfonylurea treatment, metformin does not encourage weight gain. In fact, some patients lose weight on metformin therapy. Metformin is effective when given twice daily. An extended-release, once-daily preparation has recently been introduced.

2.2.2 Thiazolidinediones (pioglitazone, rosiglitazone)

This class of agents works not by increasing insulin secretion but, rather, by increasing insulin sensitivity. However, metformin and thiazolidinedones have different mechanisms of action because they synergistically improve glycemic control when given together.[11] Thiazolidinediones appear to activate peroxisome proliferator-activated receptor PPAR-gamma, which is involved in the metabolism of lipids and the differentiation of adipocytes. There is an interaction with the retinoid X receptor RXR to produce an activated heterodimer.[12] Unlike other antidiabetic agents, the thiazolidinediones have a very slow onset of action. Although effects begin within 2 weeks, the maximal benefit of treatment is not seen for about 3 months.[13] When combined with insulin or with sulfonylureas, the onset and peak effect occur more rapidly, perhaps within 4 weeks.[14,15]

Troglitazone was the first thiazolidinedione to reach the market. Unfortunately, troglitazone showed hepatic toxicity.[16] In a small number of patients, severe liver damage occurred. As a result of this liver toxicity, troglitazone was withdrawn from the market. Rosiglitazone and pioglitazone followed troglitazone. Neither agent is toxic to the liver.[17] Rosiglitazone is the most potent thiazolidinedione with a maximal effective dose of 8 mg daily[18] as compared with 600 mg of troglitazone and 45 mg of pioglitazone. Carcinogenesis has been a concern with these agents in animal studies. Troglitazone produced lipoangiosarcomas in mice. Pioglitazone was associated with bladder cancer in rats. Rosiglitazone has shown no animal carcinogenesis in preclinical studies. Thiazolidinediones are effectively used as single agents, but their relatively slow onset of action

means that other agents are generally preferred as the first treatment of poorly controlled diabetes. Thiazolidinediones are very effective in combination use with other agents. Rosiglitazone or pioglitazone reduce HbA1c by about 1% in patients treated with either a maximal dose sulfonylurea or a maximal dose metformin, or with insulin treatment.[19,20] This same reduction of HbA1c appears to hold when a thiazolidinedione is added to an existing combination of metformin and glyburide.[21]

All thiazolidinediones cause weight gain. This weight gain is partially due to fluid retention. An increase in plasma volume results in a small drop of about 1% in hematocrit. In some susceptible patients, fluid retention may trigger congestive heart failure. This phenomenon occurs far more frequently in insulin-treated patients receiving a thiazolidinedione. There is also increased adiposity, although some studies suggest relative sparing of visceral fat. All thiazolidinediones cause a slight increase in low-density lipoprotein (LDL) levels and a substantial increase in high-density lipoprotein HDL levels. Thus, the LDL-to-HDL ratio actually decreases. There is also a slight lowering of blood pressure. As single-use agents, the thiazolidinediones do not cause hypoglycemia. They are entirely safe in patients with renal impairment. Careful, long-term echocardiographic studies in troglitazone-, rosiglitazone-, and pioglitazone-treated patients have shown no adverse cardiac effects.[22]

2.3Disaccharides Inhibitors

Type 2 diabetes results from resistance to insulin effects coupled with a relative deficiency of insulin secretion. The most characteristic abnormality of insulin production is a reduction in the early-phase release of insulin from the pancreas. Absorption of carbohydrates requires the eventual breakdown of disaccharides to form single sugars by the enzymes in the brush border of the small intestine. Disaccharidase inhibitors, such as acarbose and miglitol, effectively compensate for defective early-phase insulin release by inhibiting the breakdown of disaccharides to monosaccharides in the intestinal epithelium. Consequently, there is delayed and decreased absorption of these sugars.[23,24] Thus, there is a lower glycemic peak, permitting the diminished early-phase insulin secretion to cope more effectively with glucose disposal. The result is a decrease in postmeal glucose peaks in diabetic patients. The efficacy of acarbose and other disaccharidase inhibitors is limited by the adverse reactions caused by a large amount of nonabsorbed disaccharides in the intestinal tract. This situation is one of effective malabsorption with the attendant symptoms of flatulence, abdominal discomfort, and diarrhea. As the dose of the disaccharidase inhibitor is increased, the level of nonabsorbed disaccharides rises, leading to worsening malabsorption symptoms. However, increased disaccharide concentration leads to the induction of disaccharidases in the jejunum and ileum. Eventually, this induction of new enzymes results in a slower, smoother absorption of disaccharides. The slower absorption is still effective in reducing postprandial glucose levels, but with fewer malabsorptive symptoms. Therefore,

disaccharidase inhibitors must be started at a very low dose, with small increments over time. When started at a low dose with slow increases, the adverse reactions are minimized. Even so, the gastrointestinal adverse reactions of acarbose or miglitol occur in up to 40% of patients. Despite these limiting adverse reactions, the disaccharidase inhibitors have an advantage in terms of safety. They do not cause hypoglycemia. They do not undergo renal excretion, so that they are safe in patients with a modest elevation of serum creatinine. The disaccharidase inhibitors are effective as single agents for the treatment of diabetes and are effective in combination with sulfonylureas or insulin.

2.4 New drug modalities Incretins exendin-4, liraglutide, vildagliptin, sitagliptin

The small intestine secretes glucagon-like peptide-1(GLP-1) as well as glucose-dependent insulinotropic polypeptide (GIP, previously called gastric inhibitory peptide) in response to food intake. These hormones stimulate insulin secretion, insulin gene expression and pancreatic beta-cell growth. Furthermore, they mediate the incretin effect which augments insulin secretion following oral administration of glucose. The GLP-1 molecule is subject to rapid degradation by the DPP-IV (dipeptidyl peptidase) enzyme. Patients with type 2 diabetes have greatly impaired or absent incretin-mediated insulin secretion due to a decrease in the level of GLP-1 which leads to a decrease in glucose-dependent secretion of insulin by the pancreatic beta-cells.[25,26] Several therapeutic strategies are currently undergoing clinical trials, namely:

- enzyme-resistant GLP-1 analogues exendin-4
- albumin-bound GLP-1 derivatives liraglutide
- DPP-IV enzyme inhibitors vildagliptin, sitagliptin
- Exendin-4 exenatide

This molecule was originally isolated from the venom of the Gila monster and has a synthetic version (exenatide). The synthetic 39-amino acid peptide sequence overlaps with that of GLP-1, but has a longer half-life than native GLP- 1. This 'incretin mimic' improves glycaemic control mainly by stimulating glucose-dependent insulin secretion and suppressing postprandial glucagon secretion. It also delays gastric emptying, reduces food intake and facilitates weight loss. It is given as a twice-daily subcutaneous injection and can decrease HbA1C levels by a further 1% if given in combination with other drugs. Once-daily injections did not achieve satisfactory control in clinical trials.[27]

2.4.1 Liraglutide

This drug is currently in phase III of clinical development. The results look extremely promising. This drug, given as a once-daily subcutaneous injection, has a plasma halflife of 12 hours. [28]

2.4.2 Vildagliptin

This drug is taken in oral form as a once-daily dosage. Inhibition of dipeptidyl peptidase-IV (DDP-IV) stimulates the secretion of insulin in a glucose-dependent fashion, so minimising possible hypoglycaemic side-effects. Inhibition of DDP-IV is dose-dependent. Recent data suggest restorative

effects on pancreatic islet cells, thereby fuelling the hope that the DDP-IV inhibitors could potentially slow or reverse the course of beta-cell failure.[29,30,31]

2.4.3 Sitagliptin

This drug is also a DDP-IV inhibitor and can be used as monotherapy in type 2 diabetes or in combination with metformin, the SUs or the TZDs if the existing regimen no longer provides adequate glycaemic control. It has not yet been studied in combination with insulin. Sitagliptin is taken orally and has been shown to reduce HbA1C levels by 0.6 - 1%.

2.4.4 Amylin analogues Pramlintide

Human amylin is a 37-amino acid glucoregulatory peptide that is co-secreted with insulin by the pancreatic beta-cells. Pramlintide, a synthetic analogue, exerts its effect by slowing down gastric emptying and increasing satiety. Post-prandially, it decreases glucose levels and reduces the reintroduction of glucose in the circulation. Pramlintide is administered as a subcutaneous injection immediately before a meal. The peptide undergoes renal clearance and has a t½ of 50 minutes. It is well tolerated and is not associated with the risk of hypoglycaemia.[32,33]

3.0 CHANGES IN DRUG MANAGEMENT OF DIABETES

For many years, there were few pharmaceutical options for the treatment of type 2 diabetes. Now, new sulfonylureas, metformin, the disaccharidase inhibitors, the thiazolidinediones, and meglitinides have rapidly become available. It is hoped that the new agents will lead to improved diabetic control and a lower incidence of diabetic complications, and, ultimately, to lower mortality. The Diabetes Control and Complications Trial in the United States and the Swedish Diabetes Intervention Study have pointed to a reduction of microvascular disease in type 1 diabetes with an improvement in glycemic control.[34,35] However, the majority of diabetic patients have type 2 diabetes. Large-vessel disease affecting the coronary, cerebral, and peripheral arteries is a much more significant source of morbidity and mortality in this older population than microvascular disease.[36] Although improved glycemic control is associated with a reduced risk of coronary artery disease, concurrent improvement also occurs in the associated factors of obesity, hypertension, and dyslipidemia. It is not entirely clear how much of the reduction in cardiovascular risk is due to better glucose levels as opposed to the concurrent improvement in the associated risk factors.[37,38] The results of the United Kingdom Prospective Diabetes Study UKPDS have shed some light on these issues.[39,40] The most important result was to show the equivalence of sulfonylureas, metformin, and insulin therapy in the end points of the study, including diabetic complications and overall mortality. Thus, the findings of the UGDP study were not duplicated. However, the complexity of the study design has led to much controversy over the interpretation of the results. In particular, metformin therapy showed a clear superiority in outcomes over sulfonylureas and insulin in obese patients. However, patients in whom metformin was added to sulfonylurea treatment in an attempt to improve glycemic control actually showed

higher mortality than if sulfonylureas were simply maintained. These contradictory findings leave some uncertainty in the interpretation of the results. One of the major lessons of the UKPDS was to demonstrate that treatment of non-insulin-dependent diabetes with a single agent is not sufficient to attain the target goal of normalization of HbA1c. Patients in the UKPDS started at an HbA1c level of about 7%. Although the level of attained benefit in the pharmacologically treated group as compared with the diet-treated group was 0.9%, there was still a deterioration over 10 years to 7.9%, with no advantage for any one pharmacologic group.[41] Clearly, these levels are far from the target of normal HbA1c. No one drug is capable of normalizing HbA1c in the vast majority of patients. This is particularly true in view of the progressive deterioration in control demonstrated in monotherapy in the UKPDS. However, each class of drugs shows additive benefits when added to other classes. Fortunately, metformin and the thiazolidinediones each reduce insulin resistance by different synergistic mechanisms. The combination of metformin and rosiglitazone has shown particular strength in combined treatment. The addition of sulfonylurea adds increased insulin secretion to the benefits of decreased insulin resistance. There is now increasing usage of multiple drugs in the treatment of type 2 diabetes. This change in physician perspective is due to acceptance in the medical community of the belief that even limited abnormalities of serum glucose are harmful. The UKPDS demonstrated a definite advantage of pharmaceutical management. In addition, many of the new drugs offer less risk of hypoglycemia than the sulfonylureas. Metformin, disaccharidase inhibitors, and thiazolidinediones do not provoke hypoglycemia unless coupled with the use of sulfonylureas or insulin. The new insulin secretagogues have a lower incidence of hypoglycemia because their action is mainly during and shortly after a meal.

The use of 3 or more drugs in combination is even now becoming commonplace. Oral hypoglycemics have always offered a needleless alternative to insulin therapy. Thus, patients have accepted regimens with multiple oral agents as a refuge from insulin treatment. However, it is very useful to support the effects of oral insulin sensitizers, such as metformin and the thiazolidinediones, with an augmentation of serum insulin levels. In this respect, sulfonylureas can only achieve limited improvement in endogenous insulin secretion. There are 2 developments that may help increase the acceptability of insulin treatment. One is the development of glargine insulin. This synthetic insulin achieves very stable baseline insulin levels over a 24-hour period. Thus, a once-daily injection may suffice to augment insulin levels to a range in which insulin sensitizers can then achieve normoglycemia.[42] The second promised change in insulin treatment is inhaled insulin. The extensive lung surface permits a significant absorption of insulin. Several studies have now shown that inhalation of insulin before a meal can reduce glucose excursions as much as does injected insulin. Type 1 diabetic patients still require injections to provide a basal insulin level, which is then augmented by inhaled insulin. However, type 2

diabetic patients typically have significant basal insulin secretion. The use of inhaled insulin at meals could provide the necessary boost to allow insulin sensitizers, such as metformin and the thiazolidinediones, to maintain glucose control. If inhaled insulin does not show long-term deterioration of lung function, then the combination of inhaled insulin with insulin sensitizers will have a significant impact on glucose control.

It is expected that the new regimens will permit normal HbA1c levels to be achieved in most if not all patients. It is hoped that normalization of glycemic levels will then lead to a marked reduction in the diabetic complications that have afflicted so many people.

4.0 DIETARY MANAGEMENT OF DIABETES

4.1 Carbohydrates

Dietary carbohydrates from cereals, breads, other grain products, legumes, vegetables, fruits, dairy products and added sugars should provide 50–60% of the individual's energy requirements.[43] Both the source and the amount of carbohydrate consumed influence blood glucose and insulin responses.[44,45] Factors that influence blood glucose are not predicted by chemical composition alone; food form, ingested particle size, starch structure and cooking methods may all influence the carbohydrate absorption rate from the small intestine and the resultant blood glucose response.[46] The glycemic index (GI) expresses the rise in blood glucose elicited by a carbohydrate food as a percentage of the rise in blood glucose that would occur if the same individual ingested an equal amount of carbohydrate from white bread or glucose.[47,48] Increased use of low GI foods such as legumes, barley, pasta and whole intact grains e.g. cracked wheat may help improve blood glucose control and allow carbohydrate intake to be increased without raising serum triglycerides.[49] The role of the GI in diabetes therapy is controversial. In people with newly diagnosed type 2 diabetes, there is evidence that nutrition education based on the GI is associated with higher carbohydrate, lower fat and higher fibre intakes as well as better blood glucose and lipid control compared to those educated using traditional dietary advice.[50] Epidemiological studies also suggest that use of low GI foods reduces the risk of developing type 2 diabetes.[51,52]

4.2 Sugars

In the past, avoidance of sugar has been a major focus of nutritional advice for people with diabetes. However, research clearly shows that sugars are an acceptable part of a healthy diet for those with diabetes, particularly sugars obtained from fruits, vegetables and dairy products. Up to 10% of total daily energy requirements may consist of added sugars, such as table sugar and sugar-sweetened products, without impairing glycemic control in people with type 1[53] or type 2[54,55] diabetes. Foods containing sugars vary in nutritional value and physiological effects. For example, sucrose and orange juice have similar effects on blood glucose but contain different amounts of vitamins and minerals. Consuming whole fruits and fruit juices causes blood glucose concentrations to peak slightly

earlier but fall more quickly than consuming an equivalent carbohydrate portion of white bread. This results in a lower GI for fruits and fruit juices than bread.[56,57] Because refined sucrose produces a lower blood glucose response than many refined starches, some sweetened breakfast cereals produce lower plasma glucose and insulin responses than equal carbohydrate portions of unsweetened cereals.[58] Thus, undue avoidance of foods containing simple sugars is not necessary. Generally, however, intake of added fructose, sucrose or high-fructose corn syrup in excess of 10% of energy should be avoided, since evidence suggests that this may increase serum triglycerides and/or LDL cholesterol in susceptible individuals.[59]

4.3 Fibre

Daily soluble fibre intake of 5–10 g/d from oats, barley, legumes or purified fibre sources such as psyllium, pectin and guar, can reduce serum cholesterol by 5–10%[60,61] Purified soluble fibre sources reduce blood glucose responses and have been associated with improved blood glucose control[62] However, soluble fibre content alone is not a reliable indicator of the food's metabolic effects. The insoluble fibres from cereals may reduce the risk for coronary heart disease and type 2 diabetes by up to 30% for each 10 g increment in intake.[63]

4.4 Protein

Current evidence indicates people with diabetes have similar protein requirements to those of the general population — about 0.86 g/kg per day.[43] Although protein plays a role in stimulating insulin secretion [64,65], excessive intake should be avoided as it may contribute to the pathogenesis of diabetic nephropathy. 66 Some evidence suggests eating vegetable protein rather than animal protein is better for reducing serum cholesterol [67] and managing nephropathy.[68,69]

4.5 Fats

Numerous studies indicate high-fat diets can impair glucose tolerance and promote obesity, dyslipidemia and atherosclerotic heart disease. Research also shows these same metabolic abnormalities are reversed or improved by reducing saturated fat intake. Current recommendations on fat intake for the general population apply equally to people with diabetes: reduce saturated fats to 10% or less of total energy intake and cholesterol intake to 300 mg/d or less.[70] Scientific debate continues over which alternative is preferable to saturated fat polyunsaturated fat, monounsaturated fat or carbohydrate calories.[71,72] Research suggests monounsaturated fat such as canola, olive and peanut oils may have beneficial effects on triglycerides and glycemic control in some individuals with diabetes [73], but care must be taken to avoid weight gain. Omega-3 fatty acids, found in fish such as salmon and mackerel, may reduce serum triglycerides without impairing glycemic control.[74] Although consuming large quantities of omega-3 fatty acids from natural foods is probably not practical for most, eating fish rich in omega-3 fatty acids at least once weekly is recommended. Conversely, ingesting trans-fatty acids that are commonly found in many manufactured foods should be limited. Produced by

hydrogenating vegetable oils, the biological effects of trans-fatty acids are similar to those of saturated fat.[75,76]

4.6 Sweeteners

Moderate use of nutritive sucrose, fructose, the sugar alcohols xylitol, mannitol, sorbitol, isomalt, lactitol and maltitol and aspartame and non-nutritive sweeteners acesulfame potassium, sucralose, cyclamate and saccharin can be part of a well-balanced diet for people with diabetes.[77] The energy and/or carbohydrate content of nutritive sweeteners needs to be included in the meal plan, whereas non-nutritive sweeteners do not affect blood glucose levels and provide little or no energy. For example, aspartame is a nutritive sweetener. It provides 16 kJ/g but has a minimal energy contribution to the diet because it is extremely sweet (180–200 times sweeter than sucrose), so only a very small amount is required to sweeten a food product. Sugar alcohols raise blood glucose only minimally.[78,79] and contribute a small amount of energy to the diet. Sugar alcohols are absorbed and metabolized at different rates in the small intestine and can cause flatulence and diarrhea in some individuals.[80] During pregnancy and lactation, saccharin and cyclamate are not recommended. In moderation, acesulfame potassium, aspartame and sucralose[81] are acceptable. In individuals with phenylketonuria, the use of aspartame is contraindicated.

4.7 Micronutrients

People with diabetes should be encouraged to obtain daily vitamin and mineral requirements from a wellbalanced diet. Routine use of vitamin/mineral supplements is not recommended except in cases of inadequate food consumption or other special needs. Despite various claims concerning the benefits of supplements of vitamins and minerals in the treatment of diabetes, the evidence is not sufficient at this time to recommend routine supplementation. People with diabetes have reduced antioxidant capacity, and this may play a role in the development of complications by increasing protein glycosylation, increasing the atherogenic potential of serum LDL particles and altering endothelial function.[82] Short-term increases in plasma antioxidant capacity can be demonstrated after consumption of antioxidant vitamins such as b-carotene or vitamins C or E. However, the long-term implications of this are not clear. The Microalbuminuria, Cardiovascular and Renal Outcomes of the Heart Outcomes Prevention Evaluation study will be helpful in determining the role of vitamin E in the treatment of diabetes.[83] Decreased magnesium stores are correlated with poor diabetic control, insulin resistance, macrovascular disease and hypertension[84], but the low magnesium status may be the result rather than the cause of these conditions.

There is insufficient evidence that magnesium supplements improve blood glucose control. Chromium deficiency can result in decreased glucose tolerance but is believed to be rare.[85] Most studies have not shown any benefit from chromium supplements, possibly because of inadequate doses or

the use of poorly absorbed forms of the mineral.[86] A recent study showed that chromium picolinate significantly improved glycemic control in people with diabetes.[87]However, the doses used, 3.84 and 19.2 μmol (200 and 1,000 μg of elemental chromium) per day, were higher than the upper limit of the estimated safe and adequate daily intake.

5.0 MANAGEMENT BY PHYSICAL ACTIVITY

The multiple health benefits and improved sense of wellbeing that physical activity provides are well known.[88,89] For people with type 2 diabetes, increasing physical activity can also increase insulin sensitivity, thereby improving glycemic control. This may lessen or eliminate the need for medication.[88] People with type 1 diabetes can also enjoy the benefits of physical activity, although the effect on glycemic control will vary among individuals.[89] Physical activity can also benefit the person with diabetes by aiding in weight loss. Weight loss in itself can often decrease blood glucose. However, regardless of weight loss, physical activity may require the adjustment of insulin and/or insulin secretagogues as well as carbohydrate intake depending on the person's weight goal and personal choice. For example, for people attempting weight loss by initiating or increasing physical activity, diabetes medications may need to be decreased to avoid hypoglycemia, since increasing food intake would be counter-productive. Those requiring diabetes medications must also be aware that the glucose-lowering effects of physical activity can last or occur up to 12–24 hours or more after the activity. Thus, medications and/or food intake may need to be adjusted after physical activity, not just before it. Frequent blood glucose monitoring should aid any adjustments. Individual tolerance of physical activity, concomitant physical or medical conditions and diabetes control should be assessed prior to the health care team recommending an appropriate program of physical activity.[90]

6.0 MANAGEMENT BY HERBAL MEDICINES

6.1 Herbal medicines

Recently there has been a shift in universal trend from synthetic to herbal medicine, which we can say 'Return to Nature'. Medicinal plants have been known for millennia and are highly esteemed all over the world as a rich source of therapeutic agents for the prevention of diseases and ailments. Nature has bestowed our country with an enormous wealth of medicinal plants; therefore India has often been referred to as the Medicinal Garden of the world. Countries with ancient civilizations such as China, India, South America, Egypt, etc. are still using several plant remedies for various conditions. In this regard India has a unique position in the world, where a number of recognized indigenous systems of medicine viz., Ayurveda, Siddha, Unani, Homeopathy, Yoga and Naturopathy are being utilized for the health care of people. No doubts that the herbal drugs are popular among rural and urban community of India. The one reason for the popularity and acceptability is belief that all natural products are safe. The demand for plant based

medicines, health products, pharmaceuticals, food supplement, cosmetics etc are increasing in both developing and developed countries, due to the growing recognition that the natural products are non-toxic, have less side effects and easily available at affordable prices.[91]

6.2 Global Market for Herbal Medicines

The global market for herbal medicines currently stands at over $60 billion annually. The sale of herbal medicines is expected to get higher at 6.4% an average annual growth rate.[92] Due to the contribution of numerous significant factors, the market of herbal medicines has grown at an expressive rate worldwide. Some of them are: preference of consumers for natural therapies; concern regarding undesirable side effects of modern medicines and the belief that herbal drugs are free from side effects, since millions of people all over the world have been using herbal medicines for thousands of years; great interest in alternative medicines; preference of populations for preventive medicine due to increasing population age; the belief that herbal medicines might be of effective benefit in the treatment of certain diseases where conventional therapies and medicines have proven to be inadequate; tendency towards self-medication; improvement in quality, proof of efficacy and safety of herbal medicines and high cost of synthetic medicines.[93] According to World Health Organization, herbal medicines are lucrative globally and they represent a market value of about US$ 43 billion a year.[94] According to an estimate in 1991, the herbal medicine market in the European countries was about $ 6 billion, with Germany accounting for $ 3 billion, France $ 1.6 billion and Italy $ 0.6 billion while in other countries was 0.8 billion. In 1996, the herbal medicine market in the European countries was about $ 10 billion, in USA about $ 4 million, in India about $ 1.0 billion and in other countries was $ 5.0 billion. [95] In 1997, the European market alone reached about $ 7.0 billion. The German market corresponds to about 50% of the European market, about $ 3.5 billion. This market is followed by France, $ 1.8 billion; Italy, $ 700 million the United Kingdom, $ 400 million; Spain, $30 million; the Netherlands, about $ 100 million.[96] Presently, the United States is the largest market for Indian botanical products accounting for about 50%of the total exports. Out of this, only 40% is value addition and 60% is export of raw medicinal plant. Hence it is proposed that in future we should decrease exporting raw medicinal plant and export only value added products to realize higher earnings. Japan, Hong Kong, Korea and Singapore are the major importer of traditional Chinese medicines taking 66% share of china's botanical drug export. Globally, there have been concerted efforts to monitor quality and regulate the growing business of herbal drugs and traditional medicine. Health authorities and governments of various nations have taken an active interest in providing standardized botanical medication United States congress has fuelled rapid growth in the nutraceutical market with passage of Dietary Supplement Health & Education Act in 1994. US food and drug administration (FDA) has recently published the International Conference on Harmonization guidance common technical

Document addressing concerns related to quality of medicines that also include herbals.[97] The National Centre for Complimentary and Alternative medicine has been inaugurated as the United States Federal Government's lead agency for scientific research in this area of medicine World Health Organization WHO is also been regarding traditional medicine and has been active in creating strategies, guidance and standards of botanical medicines.[98,99] Thus the global scenario illustrates vividly both promise and challenges presented by traditional medicines.

6.3 Need of Standardization

Every Herbal Formulation must be standardized as per WHO guidelines [100] The objective of WHO guidelines is to define basic criteria for the evaluationof quality, safety and efficacy of drugs herbal medicines.[101] India is one of the world's twelve leading biodiversity centers with the presence of over 45,000 different plant species, out of this about 15,000-20,000 plants have good medicinal properties of which only about 7,000-7,500 are being used by traditional practitioners. The Siddha system of medicine uses around 600, Ayurveda 700, Unani 700 and modern medicine about 30 plants species. Projection is being made that after information technology, herbal technology will be India's biggest revenue earner.[102]

India has a great role to play, as supplier of herbal products not only to meet the domestic needs, but also to take advantage of the tremendous export potential.[103] An estimate of WHO demonstrates about 80% of world population depends on natural products for their health care, because of side effects and high cost of modern medicine.[104]

6.4 Safety and Quality of herbal drugs:

In India, about 9000 licensed units manufacture traditional medicines with or without proper standardization.[105] Most of the Indian manufactures do not follow WHO guidelines for quality control. Thus, adulteration of market samples remains a major problem in domestic and export market of Indian herbal products. Therefore, the government of India has promulgated GMP regulations for traditional systems of medicines to improve the quality and standards of Ayurvedic, Siddha and Unani drugs in Pharmacies. New rules regarding essential infrastructure manpower and quality control requirements came into force from 2000 and form part of the Drugs and cosmetic Act 1940.[106] Licensing of Ayurvedic medicine is also governed under Drug and Cosmetic Act 1940. Ayurvedic patent and proprietary medicin need to contain only the ingredients mentioned in the recommended books and specified in the Act. For any new herbal medicine, safety and efficacy data are mandatory.

7.0 Conclusion

A comprehensive herbal drug therapeutic regimen thus offers time tested safe and effective support to conventional therapy in management of diabetes.This is the combination with adequate dietary management, drug management and physicial activity would provide an integrated approach to the management of type 2 diabetes. Additoinally due to unlimited potential of herbal drug for innovative bio

active molecules, all efforts should be made to adopt a package of best practices encompassing conservation, cultivation, quality control, standardization, research and development for medicinal plants.

LIST OF SOME MEDICINAL PLANTS USED AS ANTIDIABETICS

Botanical Name	Common Name	Family	Parts Used	Active Constituents
Acanthopanax senticosus	Devil's root, touch-me- not	*Araliaceae*	Leaves	Saponins- acanthopanaxosides A,B,C
Achyranthes aspera	Devil's horsewh ip. Prickly chaff flower	*Amaranthaceae*	Whole plant	------
Acrocomia mexicana	Corojo palm	*Leguminosea*	Roots	Tetrahydropyran
Aegle marmelose	Bilwa, bael fruit, Bengal quince	*Rutaceae*	Leaf extract	Carbohydrates. Ascorbic acid.
Aesculus hippocastanum L.	Common Horse-chestnut	*Hippocastanaceae*	Seeds	Five triterpene oligologlycosides named escins-I a, I b, II a, II b, and IIIa
Agrimony eupatoria L.	Agrimony	*Rosaceae*	Whole plant	---
Allium cipa L	Onion	*Liliaceae*	Bulb	S-methyl cysteine sulphoxide
Allium sativum L.	Garlic	*Liliaceae*	Bulb	A sulphur containing amino acid and a precursor of allicin and garlic oil –S- allyl cysteine sulphoxide, and ajoene.
Aloe barbadensis Mill.	Barbados	*Liliaceae*	Exudates of leaves	Bitter principles
Annona squamosa	Custard apple, sugar apple, sharifa	*Annonaceae*	Fruit pulp	----
Anthocleista voglii	Cabbage tree	*Logoniaceae*	Root	-------
Aralia cachemirica Decne	Spikenard	*Araliaceae*	Root	----
Artemisia herbaalba	White wormwood	*Compositae*	Aerial Parts	-----
Asparagus adscendens	Shweta musli, Sufed musli	*Asparagaceae*	Root	----
Asteracantha longifolia Nees.	Kokilakchha	*Acanthaceae*	Whole plant	----
Astragalus membranaceus	Milk –Beteh Root	*Leguminosae*	Whole plant	Isoflavones-especially biochanin A
Atrocarpus heterophyllus Lam.	Jack fruit	*Moraceae*	Leaves	--
Azadirachta indica	Neem, Indian liliac	*Meliaceae*	Leaf, bark, flowers, seed.	Bitter principles-nimbin. Nimbinin. Nimbidin 47
Azorella compacta phil	Llareta	*Umbellifeare*	Whole plant	Diterpenoids-mulinolic acid, azorellantol and mulin-11, 13-dien-20-oic acid

Bambusa vulgaris	Feathy bomboo	*Gramineae*	Whole plant	----
Bauhinia candicans	White orchid tree	*Leguminosae*	Dried leaves	----
Beta vulgaris var. Cicla L.	Leaf beet, Sugar beet	*Chenopodiaceae*	----	Betavulgarosides I,II,III,IV and oleanolic acid oligoglycosides
Bidens pilosa	Harry beggarticks, cobbler's pegs, Spanish needle	*Asteraceae*	Aerial part	Polyacetylenic glucosides
Brassica juncea	Leaf Mustard	*Brassicaceae*	---	----
Brickellia veronicaefolia A. Gray	Brickellbush	*Asteraceae*	Leaves	Flavone namely 5,7,3-trihydroxy -3,6,4- trimethoxy flavone.
Bryonia alba	Native Armenian plant	*Cucurbitaceae*	Root	Trihydroxyoctadecadienoic acid
Butea monosperma	Palush, bastard-teak, flame-of-the-forest	*fabaceae*	Flower	Phytochemical substances
Cajanus cajan Millsp.	Pigeon pea	*Fabaceae*	Seed	----
Camellia sinensis L	Black tea	*Theaceae*	Leaves	Polyphenolic compounds
Cantharanthus roseus	Vinca rosea	*Apocynaceae*	Leaves	---
Cassia auriculata	Mature tea tree, avaram	*fabaceae*	Seed, flower, buds.	Tannins
Chamaemelum nobile	Chamomile, manzanilla, lawn chamomile	*Compositae*	----	3-hydroxy-3methylglutaric acid HMG containing flavonoids, glucoside-chmaemeloside.
Cinnamomi cassiae	.Cinnamon	*Lauraceae*	Bark	----
Citrullus colocynths Schard	Bitter apple, Bitter cucumber	*Cucurbitaceae*	Rind of the plant	Glycosides and saponins
Coccinia indica	Ivygourd, Tendli	*Cucurbitaceae*	Fruits juice of leaves, fruits, stem or roots	Glucoside alkaloids, glucokenin
Cocos nucifera	Coconut fiber	*Arecaceae*	----	Neutral detergent fiber
Coscinium fenestratum	Tree turmeric, Columbo Weed	*Menispermaceae*	Infusion/ tincture	Berberines and saponins
Croton cajucara Benth	Dragon's blood, sacaca	*Euphorbiaceae*	Bark	Trans-dehydrocrotonin t-DCTN a 19-nor clerodane diterpene.
Cryptolepis sanguinolenta	Nibima, kadze and gangamau	*Asclepiadaceae*	Root	Cryptolepine- an indoloquinolone alkaloid
Cuminum cyminum L.	Jera	*Apiaceae*	Fruit	----
Equisetum myriochaetum	Scouring Rush	*Equisetaceae*	------	3 kaempferol glucosides and one caffeoyl glucoside
Eriobotrya japonica Lindl.	Loquat	*Rosaceae*	----	Sesquiterpene glycoside. 3 and polyhydroxylated triterpenoids 5 and 6

Eruka sativa	Arugula, roquette	*Brassicaceae*	Seed	----
Eucalyptus globules Labill.	Tasmanian Bleu gum	*Myrtaceae*	Leaves	-----
Eugenia Jambolama	Gambol, Jamun, Black plum, bery, Jambul.	*Myrtaceae*	Pulp/Seeds	Jamboline-a glucoside
Ficus bengalensis	Banyan tree	*Moraceae*	Bark infusion	Dimethoxy derivative of perlargonidin-3-o-α-L-rhamnoside, glucosides of leuco perlargonidin
Ficus carica L.	Common fig	*Moraceae*	Leaves	----
Garcinia lola Guttiferae	Bitter-kola, Malabar tamarind, false kola	*Clusiaceae*	Seed	Kolaviron. A biflavonoid complex
Glossostemon bruguieri Desf.	Moghat	*sterculiaceae*	Root	---
Gymnema sylvestre	Gurmar. Small Indian ipecacuanha. Periploca of the woods	*Asclepiadaceae*	Leaves, stem	Gymnemoside a and beta-gymnemic acid V and a peptide Gurmarin
Helicteres isora	Bhendu, Jonkaphal, Murdasing. Marophali. East. Indian screw tree. Murva	*sterculiaceae*	Bark	Tritepenoids, a-amyrin B-amyrin, lupeol and its acetate, friedelin, B-sitosterol, epifriedelinol, bauerenol acetate, and taraxerone.
Kalopanax pictus Nakai	Castor-leaved aralia	*Araliaceae*	Stem bark	Kalopanax saponin A. hederagenin glycosides
Kochia scoparia	Tonburi, Sunner cypress Japanese fruit burning bush	*Chenopodiaceae*	Whole plant	Momordin 1 and 2'O-β-D-glucopyranoside with 3 saponins named scoparianosides A,B and C
Lagerstroemia speciosa Pers.	Queen carpe-myrtle. Banaba/Queen flower	*Lythraceae*	Leaves	Two terpenoides- colosolic acid and maslinic acid
Lantana camara	Lantana, red sage, shrub verbena	*Verbenaceae*	Juice of leaves	------
Laportea ovalifolia	Wood nettle	*Urticaceae*	Whole plant	---
Larrea tridentate	Croosote bush	*Zygophyllaceae*	Whole plant	Masoprocol
Mangifera indica	Mango	*Anacardiaceae*	Extract of leaves	----------
Memecylon umbellatum	Delek air tree. Ironwood tree Anjan. Kaya	*Melastomaceae*	Leaves	-----
Momordica charantia	Karela. Bitte gourd, balsam pear	*Cucurbitaceae*	Fruits, leaves and roots	Momordicine-a bitter glucoside, charantin, vicine, and polypeptide-p
Morus alba L	Folium mori, mulberry leaves	*Moraceae*	-----	---
Mucuna pruriens	Velvet bean or	*Fabaceae*	Seeds	D-chiro-inositol and its two

	cowhage			galacto-derivatives
Musa sapientum Kuntze	Banana	*Musaceae*	Fruits / flowers	Tannins.
Nelumbo nucifera Gaerth	East Indian lotus	*Nymphaeceae*	Finely pulverized rhizomes	---
Ocimum album Roxb.	Holy basil	*Lamiaceae*	Leaves	Volatile oil.
Ocimum sanctum Linn.	Tulsi	*Lamiaceae*	Leaves and leaf powder	Volatile oil
Olea europea L.	Olive leaf	*Oleaceae*	Leaf	Oleurpeoside
Opuntia ficus	Indian Fig	*Cactaceae*	Stems	----
Ountia steptacantha	Nopal	*Cactaceae*	Leaves and Stems	fiber and pectin
Paeonia lactiflora Pall.	Chinese peony	*Ranunculaceae*	Dried roots	8-dibenzoyl paeoniflorin and paeoniflorin
Panax ginseng	Asiatic ginseng	*Araliaceae*	Roots	Ginseng polypeptides and polysaccharides, Dammarane saponins: Protopanaxatriols, including ginsenosides RG1, RG2, Fr, Re and potopanaxadiols ginsenosides Rc, Rd, Rb1, Rb2
Pandanus odorus	Toei-hom, screwpine	*Pandanaceae*	Roots	4- hydroxyl benzoic acid
Petiveria alleaceae L.	Anamu	*Phytolacaceae*	Leaves and stem poweder	-----
Phullanthus amarus	Bhui amla, Jaramla, Bhumiamalaki	*Euphorbiaceae*	Whole plant	Tannins, flvonoids
Phyllanthus fraternus	Bhui amla, Jaramla, Jangli amli	*Euphorbiaceae*	Whole plant	Tannins, flvonoids
Piper betle	Betel, Betel pepper, Betelvine, Betel vine pan.	*Piperaceae*	Leaf	Tannins
Piper sarmentosum Roxb.	Chaplu	*Piperaceae*	Whole plant	----
Plantago ovata	Desert Indian wheat. Blond psyllium. Ispaghul plantain	*Plantaginaceae*	Aqueous extract of husks	Mucilage.
Plantago psylium L.	Sand plantain	*Plantaginaceae*	Husk	Mucilage
Psidium guajava	Guava, apple guava Kuawa. Puawa, sand plum	*Myrtaceae*	Leaves	Tannis
Pterocarpus marsupium	Vijayasar	*Leguminosea*	Heart Wood	Rich source of polyphenolic constituents namely marsupsin, pterosupin, pterosilbene and - epicatechin
Punica gratum L,	Gulnar farsi	*Punicaceae*	Flowers	----

Rhodiola sachalinensis	---	*Crassulaceae*	Roots of the plant	-----
Salacia oblonga Wall.	Saptrangi, Ponkoranti	*Hippcrateaceae*	Root bark	α- glucosidase inhibitor called kotalanol
Salacia reticulate Wright	Vairi, Pitika	*Hipperateaceae*	Dried roots and stems	α – glucosidase inhibitor called kotalanol
Salicomia hervacea L.	Marsh samphire. Saltwort, carb grass	*Chenopodiaceae*	Whole plant	-----
Salvia officinalis	Common sage, Broadleaf Sage, Garden Sage, Kitchen Sage	*Labiatae*	Sage tea	-----
Scoparia dulcis	Sweet broomweed,licoric e weed	*scrophulariaceae*	Whole plant	----
Selaginella tamariscina Beauv.	Little Club Moss	*Lycopodiaceae*	Whole plant	-----
Semecarpus anacardium Linn.	Varnish tree, dhobi-nut, markingnut, oriental caspew, bhilarva	*Anacardiaceae*	Dried nuts	----
Silybum mariamun	Milk Thistle	*Asteraceae*	Fruits, seeds and leaves	Silymarin which is composed of 3 main constituents – silybin, silychristine and silidianin
Solanum lycocarpum St. Hill	Fruit for Wolves, wolf-fruit, wolf-apple	*Solanaceae*	Whole plant	-----
Spergularia purpurea	Sandspurry	*Caryophyllaceae*	Whole plant	----
Stevia rebaudiana Bertoni	Honey grass, sweet plant. Sugar leaf, Candyleaf	*Asteraceae*	Leaves	Stevioside, a glycoside
Strobilanthes crispus	-----	*Acanthaceae*	Fermented and unfermented tea	Antioxidant and polyphenolic contents
Swertia chiraita	Kirata	*Gentianaceae*	Bark	Xanthone named 1,8-dihydroxy-3,5-dimethoxxy xanthone swerchirin
Swertia japonica	Javanica	*Grntianaceae*	Bark	5-xanthones, 2- triterpenoids namely bellidifolin and thysanolactone respectively.
Symplocos paniculata Thumb.Miq.	Asiatic sweetleaf sapphire-berry	*Symplocaceae*	Leaves and stems	Three ursane-type triterpenes, ursolic acid , corosolic acid and 2 alpha, 3alpha, 19alpha, 23-tetrahydroxyurs-12-en-28-oic acid
Tillandsia usneoides	Spanish Moss	*Bromeliaceae*	----	3-hydroxy-3methyl glutaric acid HMG
Tinospora	Guduchi	*Menispermaceae*	Root extract	Bitter principles

cardifolia				
Tinospora crispa	Sapari faridbuti ,heart – leaves moonseed	*menispermaceae*	Leaves	----
Trigonella foenum graecum	Fenugreek, Methi	*Leguminosea*	Leaf and seeds	Soluble dietary fibers SDF, steroid saponins extracted from seed – fenugreekine, and alkaloid- trigonelline
Viburaum dilatatum Thumb.	Gamazumi	*Caprifoliaceae*	Fruit	Cyanidin 3-sambubioside C3S and 5-caffeol quinic acid 5-CAQ
Withania somnifera Solanaceae	Ashvagandha, dunal, winter cherry	*Solanaceae*	Roots	Withanolides
Xanthocercis zambesiaca	Nyala tree / mashatu	*leguminosae*	Leaves and root	8stucturally related nitrogen containing sugars fagomine ,4-o-b-d-glucopyranosyl fagomine ,3-a-B-D-glucopyranosyl fagomine and 3-epyfagomine .
Zingiber officinalis	Ginger, calamus, sweet ginger, ginger root, sonthdried	*Zingiberaceae*	Fresh and dried root	----
Zizyplurs spina-christi	Christ-thorn	*Rhamnaceae*	Whole plant	A saponin glycoside – christinin A

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