SUMMARY

Currently, diabetes is controlled by a handful of available drugs such as oral hypoglycemic agents and insulin, but their use is going to be limited due to their own drawbacks like secondary failure of hypoglycemic drugs etc. To overcome the side effects or unwanted effects of synthetic drugs and hormones, there is a need to find safer and more effective antidiabetic drugs that can also take care of the associated disorders and can be used as maintenance therapy. Considerable research work is being carried out to find supplements to delay the onset and severity of the disease. An alternative cure, which could work through early to late stages of the disease, is needed as the effectiveness of any hypoglycemic drug in lowering blood glucose to a desired level decreases in many patients over a period of time. This may happen due to progression of the severity of diabetes or due to diminished responsiveness to the drug. This phenomenon is known as secondary failure.

Over 400 plants have been documented as being useful for control of blood glucose concentration; however, the majority of these plants have yet to be scientifically or medically evaluated as there is little or no information regarding their phytoconstituents and the pharmacological effects of these drugs on the animal models.

The three herbal drugs namely, *Cinnamomum zeylanicum* bark, *Inula racemosa* roots, and *Salvadora persica* roots were collected, authentified, extracted and fractionated in different solvents. Structural elucidation of the phytoconstituents was done by spectral data analysis and chemical reactions.

Determination of *in-vitro* and *in-vivo* antidiabetic activity of the hydroalcoholic plant extracts including parameters like blood glucose, lipid profile, glucose diffusion and *α*-glucosidase assays were carried out.

**Phytochemical investigation**

*Cinnamomum zeylanicum* known as Ceylon cinnamon is a tree that is indigenous to Sri Lanka and southern India, growing semi-wildly in moist lowlands. Spice obtained from its inner bark was the most sought after spice in Europe from the 16th to the 18th century and is a revered spice with known ancient use in the ayurvedic system.
The spectral analysis of *C. zeylanicum* bark extract resulted in characterization of new salicylaldehydic esters i.e. Tetrasalicylaldehyde myristate established as salicylaldehydic-(2-O → 6')-salicylaldehydic-(2'-O → 6'')-salicylaldehydic-(2''-O → 6'''')-salicylaldehydic tetradecanoate and Tetrasalicylaldehyde behenoate elucidated as salicylaldehydic-(2-O → 6')-salicylaldehydic-(2'-O → 6'')-salicylaldehydic-(2''-O → 6'''')-salicylaldehydic-n-docosanoate. The structure of Phenyl zeylanicaldehyde has been characterized as 11-methylene-18-aldehyde-n-tetradecenyl-2-phenol and was found to be a new phenolic derivative. Tetrasalicylaldehyde γ-fenchenyloxy capriate was characterized as salicylaldehydic-(2b-O → 6b)-salicylaldehydic-(2b-O → 6c)-salicylaldehydic-(2c-O → 6d)-salicylaldehydic-(2d-O → 2a)-γ-fenchyl-2a-oxy-8'-olyl-n-decanoate which is a new tetrasalicylaldehyde γ-fenchyl ester. Similarly Tetrasalicyloxy γ-fenchenyldioxy-arabinolinoleiate was determined to be salicylic acid-(2a-O → 6b)-salicylaldehydic-(2b-O → 6c)-salicylaldehydic-(2c-O → 6d)-salicylaldehydic-2α-oxy-γ-fenchyl-7''-ol-8''-oxymethylene-n-dec-9'', 12''-dienoate-7''-O-β-D-arabinofuranoside is a new tetrasalicylic γ-fenchyl-arabinosidic ester. A new tetrasalicylaldehydic derivative, Tetrasalicylaldehydic γ-fenchenyldioxy-arabinopalmitate has been identified as p-hydroxy-salicylaldehydic-(2a-O → 6b)-p-hydroxysalicylaldehydic-(2b-O → 6c)-p-hydroxysalicylaldehydic-(2c-O → 6d)-p-hydroxysalicylaldehydic-2d-O-2α-oxy-γ-fenchyl-7''-ol-8''-oxymethylene-n-hexadecanoate -7''-O-β-D-arabinopyranoside.

*Inula racemosa*, commonly known as ‘Pushkarmoola’, has been utilized as a therapeutic since time immemorial in both organized (Ayurveda, Unani) and unorganized (folk, tribal, native) form. The roots of *I. racemosa* have been used as folk medicine in East Asia and Europe. The spectral analysis of *I. racemosa* roots extract revealed two known compounds along with few new compounds. *n*-Decanyl docosdienoate, elucidated as (5z, 13z)-n-decanyl-n-docos-5, 13-dienoate, is a new fatty acid ester reported for the first time. A variety of new sesquiterpenic esters reported are; 15-n-Tricostrienyl eudesmalolide, formulated as 15-[(13z, 18’z, 20’z)-n-tricos-13, 18, 20-trienyl]-eudesmal-4(11), 6, 12(13)-trien-8,14-olide-15-oate; 15-Tetracosdienyl eudesmalolide characterized as 15- [(16’Z), (21’Z)-n-tetracos-16', 21'-
dienyl]-eudesmal-4(11), 6, 12 (13)-trien-8, 14-olide-15-oate; Eudesmalolide tetradehydroisophytoate established as 15-[(8'Z) (9'7)-n-2',6',10'-trimethyl-14-carboxylic acid-hexadec-7', 9'-dien-6'-oxy]-eudesman-4(II), 6, 12-trien-8, 14-olide and Eudesmalolide palmityloxy tetradehydro-isophytoate A established as 15-[(8''Z), (9'Z)-6', 10' dimethyl-14'-oic acid-17'-oxymethylene-hexadec-7', 9'-dien-6'-oxy]-eudesman-4(11), 6,12-trien-8,14-olide-17'-hexadecanoate. Eudesmalolide linolenoxy tetradehydroisophytoate characterized as 15-[(3'Z), (7'Z)-2', 6', 10'-trimethyl-14'-oic acid-16'-oxymethylene-hexadec-3', 7'-dien-5'-oxy]-eudesman-4(11), 6, 12-trien-8, 14-olide-16'-octadec-9'', 12'', 15''-trienoate; Eudesmalolide linolenoxy didehydro isophytoate was determined as 15-[(7'Z)-2', 6', 10'-trimethyl-14'-oic acid-16'-oxymethylene-hexadec-7'-en-5'-oxy]-eudesman-4(11), 6, 12-trien-8, 14-olide-16'-octadec-9'', 12'', 15''-trienoate and finally Eudesmalolide palmityloxy tetradehydroxy-isophytoate B, characterized as 15-[(3'Z), (7'Z)- 6', 10'-dimethyl-14'-carboxylic acid-17'-oxymethylene-hexadec-3', 7'-dien-6'-oxy]-eudesman-4(11), 6, 12-trien-8, 14-olide-17'-hexadecanoate were also characterized. These have been confirmed as new sesquiterpenic esters reported for the first time. 15-Nonadecenyl eudesmalolide has been elucidated as 15-[(16z)-n-monadec-16'-enyl]-eudesmal-4(11)6, 12(13)-trien-8,14-olide-15-oate and 15-Tetracosenyl eudesmalolide established as 15-[(16'Z)-n-tetracos-16'-enyl]-endesmal-4(11), 6, 12 (13)-trien-8, 14-olide-15-oate. These are confirmed as new eudesmalolides reported from *I. racemosa*.

The traditional medicinal use of *Salvadora persica*, commonly known as tooth brush tree as antimicrobial toothbrush stick for oral hygiene, and to treat gum inflammation, is a centuries old practice and a part of Greeko-Arab system of medicine. It is also known as Arak and is the main plant used in chewing sticks from East Africa through the Asian subcontinent including Saudi Arabia. The spectral analysis of *S. persica* roots extract revealed the isolation of few known compounds along with certain new compounds.

The structure of β-Sitosteryl arabinosyl vanilloyl stearate was established as stigmast-5-en-3β-0yl-3β-D-arabinofuranosyl-2'-vanilloyl-4''-octadecanoate. It is a new steroidal glycosidic ester. As per the evidences, two new steroidal ester have been confirmed i.e. β-Sitosteryl-3-vanilloyl-4'-palmitate characterized as stigmast-5-en-3β-0yl vanilloyl-4'-hexadecanoate and β-Sitosteryl vanilloyl oleate determined as stigmast-5-en-3β-0yl-3'-
methoxy-4'-hydroxybenzoyl-4'-octadec-9''-enoate.
The spectral data analysis of the structure of \( \beta \)-Sitosteryl-3-vanilloyl-4''-stearate characterized as stigmast-5-en-3\( \beta \)-olyl 3'-methoxy-4'-hydroxybenzoyl-4''-octadecanoate indicates it as a new steroidal vanillic ester. The structure of Persicanyl linolenate and Persicanyl oleate has been formulated as 5'-\{(3,4-dimethoxyphenyl)-pent-cis,cis-2',4'-dienyl\}-n-octadec-9''-enoate and 5'-\{(3,4-dimethoxyphenyl)-pent-cis,cis-2',4'-dienyl-1''-n-octadec-9'', 12''-dienoate, respectively, indicating both as new fatty acid esters.
The structure of Dimethoxybenzyl diarabinostearate, a new benzyl alcohol diarabinosyl ester, has been elucidated as 3,4'-dimethoxybenzylalcohol-7-\( \beta \)-D-arabinopyranosyl-(2'\( \rightarrow \)1'')-\( \beta \)-D-arabinopyranosyl-2''-octadecanoate. A new phenyl substituted pent-dienolyl tetroglycosidic ester, Persicanyl tetra-arabinosyl stearate has been identified as 5'-\{(3, 4-dimethoxyphenyl)-pent-cis, cis-2', 4'-dien-1''-olyl-\( \beta \)-D-arabinopyranosyl-(2a\( \rightarrow \)1b)-\( \beta \)-D-arabinopyranosyl-(2b\( \rightarrow \)1c)-\( \beta \)-D-arabinopyranosyl-(2c\( \rightarrow \)1d)-\( \beta \)-D-arabinopyranosyl-2''-octadecanoate.

**Biological investigation**

*In-vitro* and *in-vivo* investigations on the plant extracts were performed to assess the anti-diabetic potentials of selected plants.

Glucose diffusion *in-vitro*: *S. persica* (50 g/l of dried plant material) caused the most significant lowering of glucose diffusion across dialysis tube walls, as compared to other drugs and control. At 60 min. the concentration of glucose was found to be 1.57±0.48 mg/dl with *S. persica* in comparison to the control at 3.72±1.35 mg/dl followed by *I. racemosa* at 6.21±2.12 mg/dl, thus confirming their glucose diffusion retarding properties. *C. zeylanicum* did not inhibit the glucose diffusion. These results suggest that part of the antihyperglycemic actions of these plants may be by decreasing glucose diffusion in the gut lumen.

\( \alpha \)-Glucosidase inhibitory activity *in-vitro*: The plant extracts exhibited \( \alpha \)-glucosidase inhibitory activity when tested at a concentration range of 1.25 to 50 mg/ml with the most noticible inhibition observed with *S. persica* extract showing 58.65±2.1% inhibition followed by *I. racemosa* extract showing 41.41±3.5% inhibition at 20 mg/ml concentration as compared to the standard which gave 72.01±3.8% inhibition at 20 mg/ml
concentration. The *C. zeylanicum* extract also showed inhibitory activity up till 10 mg/ml comparable to *I. racemosa* but the inhibition became stagnant with further increase in the concentration.

Anti-hyperglycemic activity _in-vivo_: The hydro-alcoholic extract of the plants decreased the blood glucose significantly during the course of study but an immediate and most significant decrease was observed with *S. persica* at 500 mg/kg with a significant decrease in fasting blood glucose (*P* < 0.001). *I. racemosa* 500 mg/kg also showed a significant decrease (*P* < 0.01) on the 21st and 28th day. This phenomenon clearly indicates that extracts of *S. persica* can potentially control the hyperglycemic state in diabetes.

A significant hypolipidemic effect was observed with the plants in which *C. zeylanicum* 250 mg/kg and *S. persica* 500 mg/kg were found to have the most evident reduction in cholesterol and triglycerides, (*P* < 0.001). The reduction in HDL and VLDL was non-significant by all the plant extracts.

In conclusion, *C. zeylanicum* bark, *I. racemosa* root and *S. persica* root supplementation resulted in decreased fasting blood glucose levels and improvement of lipid profile of diabetic rats, which seemed to be mediated via an increase in plasma insulin levels combined with decrease of glucose diffusion and α-glucosidase in gut lumen. Although the exact components responsible for anti-hyperglycemic and anti-hyperlipidemic properties of these extracts were not elucidated, we presume that various isolates like sterols, eudesmalolides and esters, present in the plants, to be responsible for hypoglycaemic activity. Therefore, supplementation with these plants could be beneficial for the prevention and management of diabetes by modulating the glucose and lipid metabolic enzyme activities. In future more extensive work that can be done on the new isolates obtained from these plants.