Chapter 3:
Review of literature
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REVIEW OF LITERATURE

Diabetes mellitus or Type 2 diabetes or non–insulin-dependent diabetes mellitus is a metabolic disorder of the endocrine system. The disease is found in all parts of the world and is rapidly increasing worldwide. Many of the oral antidiabetic agents such as sulfonylureas, biguanides, α-glucosidase inhibitors, and glinides, which are used as monotherapy or in combination to achieve better glycemic regulation, have a number of serious adverse effects; thus, managing diabetes without any side effects is still a challenge (Mankil et al., 2006).

Many traditional plant treatments for diabetes exist, a hidden wealth of potentially useful natural products for diabetes control. Plant based drugs have a long history in both traditional and modern societies. A number of modern drugs have been isolated or derived from natural sources based on their use in traditional medicine as herbal remedies or crude drugs, or as purified compounds approved by various regulatory agencies (Butler, 2004; Jones et al., 2006). The active principles present in the medicinal plants have been reported to possess pancreatic beta cells regenerating, insulin releasing and fighting the problem of insulin resistance (Welihinda et al., 1982).

Nonetheless, few traditional antidiabetic plants have received scientific or medical scrutiny, despite recommendations by the World Health Organization in 1980 that this should be undertaken. Various researches have been done on the medicinal plants and have been pharmacologically tested and proven to be effective as anti-diabetic drugs. Muniappan et al., 2009 evaluated the antihyperglycemic effect of scoparic acid D (SAD), a diterpenoid (Figure 3.1a) isolated from the ethanol extract of Scoparia dulcis in streptozotocin (STZ) - induced diabetic male Wistar rats. SAD was administered orally at a dose of 10, 20 and 40 mg kg$^{-1}$ bodyweight for 15 days. At the end of the experimental period, the SAD-treated STZ diabetic rats showed decreased levels of glucose as compared with diabetic control rats. The improvement in blood glucose levels of SAD-treated rats was associated with a significant increase in plasma insulin levels. The study confirmed the antihyperglycemic effect of SAD and also demonstrated the consistently strong cytoprotective properties of SAD.
Dineshkumar et al., 2010 studied the effect of mahanimbine (carbazole alkaloid from Murraya koenigii leaves) (Figure 3.1b) on blood glucose and serum lipid profiles on streptozotocin-induced diabetic rats. Diabetes was induced in adult male Wistar rats by intra-peritoneal injection of streptozotocin (45mg/kg). Mahanimbine (50mg/kg and 100 mg/kg) were administrated as a single dose per week to the diabetic rats for 30 days. Fasting blood sugar and serum lipid profiles were measured in the diabetic and non-diabetic rats. In addition, in vitro alpha amylase and alpha glucosidase inhibitory effects of mahanimbine were performed. In the diabetic rats, the elevated fasting blood sugar, triglycerides, low density lipoprotein, very low density lipoprotein levels were reduced and high density lipoprotein level was increased by mahanimbine at a dose of 50mg/kg and 100mg/kg (i.p). In addition, mahanimbine showed appreciable alpha amylase inhibitory effect and weak alpha glucosidase inhibitory effects when compared with acarbose. The study indicated that mahanimbine possess anti-hyperglycemic and anti-lipidemic effects. The results concluded that the mahanimbine has beneficial effect in the management of diabetes associated with abnormal lipid profile and related cardiovascular complications.
Dineshkumar et al., 2010 studied the anti-diabetic and hypolipidemic effects of mangiferin (Figure 3.1c) isolated from the stem bark of Mangifera indica (Anacardiaceae) in type 1 and type 2 STZ induced diabetic rats models. Mangiferin (at a dose 10 and 20mg/kg) was administrated intra-peritoneally in type 1 and type 2 diabetic rats daily up to 30 days. Biochemical parameters notably fasting blood sugar and lipid profile were estimated. In addition, in vitro alpha amylase and alpha glucosidase inhibitory effects of mangiferin were determined. Mangiferin exhibited significant (P<0.05) anti-diabetic as well as hypolipidemic effects by lowering FBS, TC, TG, LDL, and VLDL levels; but also with elevation of HDL level in type 2 diabetic model rats. In addition, mangiferin showed appreciable alpha amylase inhibitory effect. The study concluded that the mangiferin showed anti-diabetic as well as hypolipidemic potentials in type 2 diabetic model rats. Therefore, mangiferin possess beneficial effects in the management of type 2 diabetes with hyperlipidemia.

Orsolic et al., 2012 examined the antioxidant effect of water soluble derivative of propolis (WSDP) and ethanolic extract of propolis (EEP) on renal and liver function in alloxan-induced diabetic mice. Propolis is a complex resinous material collected by honeybees from buds and exudates of certain plant sources neighbouring its hives. Propolis consisting of sap, bark and bee excreta accumulates in bee hives. Propolis possesses a broad spectrum of biological activities and has a historical utilization in folk medicine. Administration of propolis to diabetic mice resulted in a significant increase of body weight, haematological and immunological parameters of blood as well as 100% survival of diabetic mice. Alloxan-injected mice showed a marked increase in oxidative stress in liver and kidney homogenate. The administration of natural antioxidants such as propolis mitigate alloxan-inuduced toxicity and increase survival times of diabetic animals and attenuates hepatotoxicity and nephrotoxicity by reducing alloxan-induced oxidative stress in a diabetic mice model. The findings
strongly suggest that oxidative stress has a pivotal role in the pathophysiology of diabetic nephropathy and hepatotoxicity and those propolis preparations are able to attenuate diabetic hepatorenal damage, probably through its antioxidative action. The study implies that propolis could be substituted as a dietary supplement to prevent or treat diabetic complications.

Therefore considering the traditional use of numerous medicinal plants in diabetes treatment, it is important to establish the various reports of research work done on these two medicinal plants namely \textit{Eurya japonica} Thunb. and \textit{Ficus auriculata} Lour. which has been undertaken to do detailed research work on these two plants.

Akira \textit{et al.}, 1989 isolated (Figure 3.1d) and structurally elucidated a new acylated flavonoid glycoside namely euryanoside with two known cyclohexanone compounds, halleridone (4) and comoside (5), from the male flowers of \textit{Eurya japonica} Thunb. (Theaceae). The structure of euryanoside has been established to be apigenin 5-O-\alpha-L-rhamnopyranosyl-(1-2)-(6"-O-acetyl)-\beta-D-glucopyranoside (1), based on the lines of chemical and spectral evidence. In their study, the structure of monoglycoside (2) and apigenin (3) were also elucidated from euryanoside. It was reported that the leaves and fruits of \textit{Eurya japonica} Thunb. (hisakaki in Japanese (Theaceae), a Chinese crude drug (ling-mu in Chinese; Reiboku in Japanese), was used in China as an anodyne for rheumatism, as a remedy for swelling, and as an external hemostatic for traumatic bleeding, etc (Chiang, 1977). They further cited that a number of flavonoids (anthocyanins) (Shibata \textit{et al.}, 1962; Terahara \textit{et al.}, 1988), flavones and flavonol glycosides (Morita \textit{et al.}, 1974), as well as a few isoprenoids (betulinic acid and \beta-sitosterol (Desai \textit{et al.}, 1976), have been isolated from fruits, leaves, and barks of \textit{Eurya japonica} Thunb.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image}
\caption{Figure 3.1d: 1: Euryanoside; 5-O-\alpha-L-rhamnopyranosyl-(1-2)-(6"-O-acetyl)-\beta-D-glucopyranoside ; 2: Monoglycoside ; 3: Apigenin ; 4: Halleridone and 5: Cornoside}
\end{figure}
Tae et al., 2011 cited that the leaves of *Eurya emarginata* and *Eurya japonica* Thunb. have been used in Korean traditional medicine to treat arthritis (Ahn, 2008). From the ethanol extract of the leaves and twigs of *Eurya emarginata*, new phenylpropanoid glycosides (Figure 3.1e), eutigosides D (1) and E (2), were isolated along with five known compounds, eutigoside B (3), eutigoside C (4), cinnamic acid (5), rengyolone (6) and cleroidindin B (7) respectively.

Chung and Epperson., 2000 reported the spatial genetic structure in an undisturbed Korean population of *Eurya japonica* Thunb. They reported that *Eurya japonica* Thunb. is pollinated by bees, mature female trees produce hundreds of fruits (ca. 3 mm to 6 mm in diameter), and each fruit (berry) has ten to 23 small seeds. *Eurya japonica* Thunb. is an economically important species in Korea, as the branches are widely used in floral tributes and wreaths.

Yun et al., 2012 studied the *in vitro* inhibitory activities of pancreatic lipase and phosphodiesterase from extracts obtained from 61 traditional Korean medicinal plants in pursuit of new sources of pancreatic lipase inhibitors from relatively safe and effective natural products. In their study it was observed that *Eurya japonica* Thunb. exhibited lipase inhibitory activity. Thus the study concluded that it is worthwhile to

![Figure 3.1e: 1: Eutigosides D; 2: Eutigosides E; 3: Eutigoside B; 4: Eutigoside C; 5: Cinnamic acid; 6: Rengyolone and 7: Cleroidindin B](image-url)
investigate further these extracts for their potential pharmacological effect in obesity *in vivo* and attempts should be made to purify their active components to be used as safer and cheaper therapeutic agents in future.

Li *et al.*, 2013 isolated and characterized four new lignans, two neolignans and two new chromone glycosides (Figure 3.1f), together with 25 known compounds and one chromone, namely 5,7-dihydroxy-4H-chromen-4-one-3-O-α-L-arabinopyranoside (Li, 2010); five lignans, tortoside E (Wang and Jia, 1997), sakuraresinol (Kiyoshi, *et al.*, 1990), (−)-2α-O-(β-Dglucopyranosyl) loniresinol (Hans, *et al.* 1997), (+)-3α-O-(β-Dglucopyranosyl) loniresinol (Hans *et al.*, 1997), and aviculin (Kim *et al.*, 1994); six flavonoids, (+)-epitaxifolin 3-O-β-D-xylopyranoside, (−)-epitaxifolin 3-O-β-D-xylopyranoside, (−)-taxifolin 3-O-β-D-xylopyranoside, (−)-taxifolin 3-O-β-D-xylopyranoside (Nonaka *et al.*, 1987), (2R,3R)-(−)-glucodistylin, and (2S,3S)-(−)-glucodistylin (Dubeler *et al.*, 1997); 11 phenyl glycosides, di-O-methylcrenatin (Li *et al.*, 2005), 2,6-dimethoxy-4-(2-hydroxyethyl) phenol 1-O-β-D-glucopyranoside (Zhang *et al.*, 2001), dihydrosyringin (Michalska *et al.*, 2010), 3,4,5-trimethoxyphenyl-β-D-glucopyranoside (Verotta *et al.*, 2001), 3,4-dimethoxyphenyl-β-D-glucopyranoside (Pan and Lundgren 1995), 3-hydroxy-4,5-dimethoxyphenyl-β-D-glucopyranoside (Takara *et al.*, 2002), cremanthodioside (Wang *et al.*, 2004), junipetriolosides A (Comte *et al.*, 1997), 6′-O-coumaroyl-1′-O-[2-(3,4-dihydroxyphenyl)-ethyl]-β-D-glucopyranoside (Es-Safi *et al.*, 2005), neocalceolarioside D (Kuwajima *et al.*, 1993), and norbergenin (Pouyssegur *et al.*, 2010); one triterpene, betulnic acid (Khan *et al.*, 2010); and one steroid, β-sitosterol glucopyranoside (Bayoumi *et al.*, 2010), from the ethanol stem extract of *Eurya japonica*. The isolates were evaluated for antioxidant and anti-NO production activities and found to possess potent antioxidant activity compared to the positive control. In the study they cited that fruits and leaves of *Eurya japonica* Thunb (Theaceae) are used in the Chinese traditional medicine “Lingmu” for the treatment of rheumatoid arthritis, tympanites, hemostasis of injuries, etc. The components of the leaves and berries of this plant also contain halleridone, cornoside, and flavonoids.
Figure 3.1f: 1: (+)-ovafolinin B-9'-O-β-D-glucopyranoside; 
2: (-)-ovafolinin B-9'-O-β-D-glucopyranoside; 
3: (+)-ovafolinin E-9'-O-β-D-glucopyranoside; 
4: (-)-ovafolinin E-9'-O-β-D-glucopyranoside; 
5: Eusiderin N; 
6: (7S, 8R)-3,5,5'-trimethoxy- 4',7-epoxy-8,3'-neolignan-9,9'-diol-4-O-β-D- 
xylopyranoside; 
7: 5, 7-dihydroxy-4Hchromen- 4-one-3-O-β-D-glucopyranoside and 
8: 5,7-dihydroxy- 4H-chromen-4-one-3-O-β-D-xylopyranoside.

Roder et al., 2003 studied the relative importance of Ficus auriculata Lour. in 
Bhutan with special reference to farmers’ preference and fodder quality. They 
reported Ficus auriculata Lour. as an important tree fodder in the Himalayan region
of Nepal and India and its fodder quality is far superior to paddy straw, the main winter fodder in the rice growing regions of the Himalayas. They concluded that it is imperative to carry out research exploring its potential in evolving production systems and to quantify the opportunities of improving its nutritional quality and productivity through selection.

Amrita et al., 2009 studied the phytochemical screening, antibacterial and antioxidant activity of the stem bark of Ficus auriculata Lour. Qualitative phytochemical analysis of methanol extracts of Ficus auriculata Lour. stem bark showed the presence of alkaloids, carbohydrates, saponins, glycosides, phytosterols, resins, phenols, tannins, diterpenes, flavonoids, proteins, and amino acids. They concluded that the stem bark of the plant extract showed potential antioxidant activity but antibacterial activity was found to be comparatively lower compared to that of the standard antibiotics used. There are reports that leave of Ficus auriculata Lour. are crushed and the paste is applied on the wounds. The plant is also used in diarrhoea and dysentery. Stem bark juice is effective for diarrhoea, cuts and wounds. Roasted figs are taken for diarrhoea and dysentery. Root latex is used in mumps, cholera, diarrhoea and vomiting. Mixture of root powder of Ficus auriculata Lour. and bark of Oroxylum indicum is taken in jaundice (Kunwar et al., 2006). Latex of Ficus auriculata Lour. is used to treat cuts and wounds, caries and also used as an anthelmintic (Manandhar, 2002).

Ripu., 2010 reported the herbal medicinal plants on the basis of treatment of most illness through traditional knowledge which are currently being screened for their therapeutic potential in far-west Nepal. In the study, they included Ficus auriculata Lour. and reported that the stem juice is considered effective against diarrhea and fruits are consumed for dysentery. Bark juice and roasted figs are useful for diarrhea and dysentery (Rajbhandari, 2001 and Manandhar, 2002). They also reported that tannins of the bark extract may reveal anti-inflammatory and analgesic activities (Okoli et al., 2003). β sitosterol, epifriedelanol, friedelin (Rastogi and Mehrotra, 1979) were the latest common pharmacological findings of this plant. Although traditional herbal medicine is only a primary means of health care in far-west Nepal, the medicine has been pursued indigenously with complementing pharmacology and the Ayurveda. Therefore, they concluded that further pharmacological evaluation of the traditional herbal medicine deserves careful attention.

Sirisha et al., 2010 studied the antioxidant activity of Ficus species with its pharmacological activities. They concluded that the Ficus species are rich source of
naturally occurring antioxidants of which phenolic compounds and flavonoids play a vital role in preventing innumerable health disorders related to oxidative stress including cardiovascular diseases, neurodegenerative diseases and cancer. Ficus species due to their strong antioxidant and biological properties are also known to diffuse the toxic free radical and can be used as a possible food additive or in nutraceutical and biopharmaceutical industries.

Sasinath., 2007 studied the general diversity of vascular plants, status of invasive alien species (IAS) and nationally threatened plant species, human use potentials of phytodiversity, and some phytodiversity-based measures to restore and improve the Ramsar characteristics of Beeshazar Lake and surrounding landscape system. This area is a part of the Barandabhar forest corridor (BFC) - an extension of buffer zone of the Chitwan National Park, Nepal. He reported Ficus auriculata Lour. is used as feed for Livestock plant species found in Beeshazar Lake system and adjoining areas of Nepal.

Ahlam et al., 2011 has investigated the bioactive compounds of Ficus auriculata Lour. plant. Eight known compounds (Figure 3.1g), including: betulinic acid, lupeol, stigmasterol, bergapten, scopoletin, β-sitosterol-3-O-β-D-glucopyranoside, myricetin, and quercetin-3-O-β-D-glucose were isolated from the petroleum ether, chloroform and ethyl acetate fractions of the alcoholic extracts of leaves and fruits of Ficus auriculata Lour. They claimed that this is the first report on compounds separation from Ficus auriculata Lour. (Moraceae). The antioxidant activity of the fruit extract was more than the leaves. This effect may be mainly due to the presence of higher flavonoids and phenolic content in the fruit (Hopia and Heinonen, 1999). The plant shows anti-inflammatory activity and this may be due to the presence of sterols and triterpenoids as betulinic acid, lupeol, stigmasterol and β-sitosterol-3-O-β-D-glucoside (Perez, 2001).
Figure 3.1g: 1: Betulinic acid; 2: Lupeol; 3: Stigmasterol; 4: Bergapten; 5: Scopoletin; 6: β-Sitosterol-3-O-β-D-glucopyranoside; 7: Myricetin; 8: Quercetin-3-O-β-D-glucopyranoside
Sarla and Subhash., 2012 studied the \textit{in vitro} antibacterial, antifungal activity, nutritional evaluation and phytochemical screening of wild edible fruit of Garhwal Himalaya. This analysis revealed that, the fruits contained higher value of fat, protein, fiber and minerals as compared to the cultivated fruits i.e. apple and mango. \textit{Ficus auriculata} Lour. fruits contain sufficient amount of nutrients, required per day per person. Consumption of fruits may promote general health and well-being as well as reduce the risk of chronic diseases. These findings confirm that the \textit{Ficus auriculata} Lour. may be potential source for the formulation of nutraceuticals or natural foods. There were reports that Ficus species are rich source of polyphenolic compounds and flavonoids which are responsible for strong antioxidant properties that help in the prevention and therapy of various oxidative stress related diseases such as neurodegenerative and hepatic diseases (Bailey and Day 1989).

The above cited literature shows certain chemical and biochemical aspects of \textit{Eurya japonica} Thunb. and \textit{Ficus auriculata} Lour. which have been studied by different workers. It is worthwhile to extend further studies on pharmacological evaluation of these traditional herbal medicinal plants and then linking of the indigenous knowledge of these medicinal plants to modern research activities in providing a new approach, which makes the rate of discovery of drugs much more effective thereby more people take up plant medicine as an alternative therapy.