Diterpenes-A Review on Therapeutic uses with special emphasis on Antidiabetic Activity

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ABSTRACT

Natural products for human well-being and as cure for diseases continue to gain importance. Complementary and alternate medicine (CAM) using natural product extracts maintaining their originally present important ingredients is getting popular due to toxicities encountered in drug discovery. Due to drying up of pipeline from big pharma industries, CAM is a sought after source for new leads in drug discovery and continues to challenge developmental food and beverage scientists. These ingredients were known to be associated with protective effect in patients suffering from cardiac or cancer diseases. Most natural foods contain Terpenoids, Diterpenes, and Tetraterpenes. Diterpenes have been used in traditional medicine for anti-cancer, anti-diabetic and various other ailments. Analysis of the structures of Diterpenes evaluated for diabetes treatment is presented with a view to kindle interest on these useful compounds, wherein a systematic evaluation and profiling is warranted that could result in finding new leads.

KEY WORDS: Diterpenes, anti-diabetic, hypoglycemia, insulin secretion, insulin release, insulin resistance, glucose reduction, Type 2 diabetes, natural products, herbal medicine

INTRODUCTION

Nutritional products for human health and treatments for diseases are ever increasing (Zhao, 2007; Black et al., 2008). Awareness for healthy food over junk food is gaining importance due to complications arising out of the newer food habits and lifestyle changes (Hardy, 2000) leading to renewed interest in the development of natural ingredients. Maintaining consistency of products offers challenges for developmental food and beverage scientists (Yach et al., 2010). Beneficial effects of fruit and vegetable based products are achieved through enriching the naturally occurring antioxidant polyphenols, terpenoids and flavonoids. These ingredients were known to be associated with protective effect in patients suffering from cardiac or cancer diseases (Deppek & Anshu 2008; Fabricant & Farnsworth 2001; Talalay, 2001). Most natural foods contain Terpenoids and they are classified as monoterpenes (like limonene, carvone or carveol), diterpenes (including the retinoids), and tetraterpenes (which include all different carotenoids like alpha- and beta-carotene, lutein, lycopene, zeaxanthin and cryptoxanthin). A review of the literature on terpenes (Roman et al., 2007; Kochhar, 2008), describes potential impact of terpenes in treatments as antioxidant, anticancer and in metabolic diseases with their mode of action. Sources for diterpenes range from fungal, plant and marine sources (Liu & Hu, 2010). Diterpenes have been used in traditional medicine for anti-cancer, anti-diabetic and various other ailments (Johnson, 2011; Trapp & Croateau 2001; Jiangsu, 1977).

Diabetes overview

Diabetes Population is steeply increasing and 6.4% of the world’s adult population (Diabetes Atlas, 4th edition: 2006. International Diabetes Federation: Brussels) is affected by diabetes. Long term diabetes patients face complications and development of T2DM (Hamiel & Zeitler, 2005) has been associated with a decrease in insulin secretion and progresses through different stages starting from insulin secretion and hepatic and peripheral insulin action. Chronically high blood glucose levels lead to insulin resistance causing B-cell dys-function in addition to insulin resistance. Current medications (Luna & Feinglos, 2001 & Ketz, 2001) address reducing glucose through increased insulin secretion, better glucose utilization & glucose absorption, reducing re-absorption of glucose from kidney, etc. Drugs available do not effectively address the problem of mealtime high glucose levels (Gerstein et al., 2008; Holman et al., 2007) that have been shown to trigger atherogenic processes. Looking at the bottom of T2DM, it is essential to improve B-cell function and mass which would enable improved insulin sensitivity and reducing insulin resistance. Human clinical data shows that intensive insulin therapy can improve B-cell function. Hence any drug that helps in improving insulin secretion will be of great help to diabetics, as is evident from the latest drug Exenatide for insulin secretion from intestine (Malhotra et al., 2008).

Diabetes medications

Analysis of the common anti-diabetic medications (Table 1), their mechanism of actions, target organs, benefits and risks has been published (Ketz 2001 & Shari, 2007). Diabetes treatment begins with stimulation of insulin production employing sulfonyl urea drugs (Simard et al., 2007) followed by addressing insulin resistance (Kobayashi 1999); Evanthis et al., (1998) with Metformin. These medications caused hypoglycemia and weight loss respectively. Acarbose, an a-glucosidase inhibitor helps reduce intestinal glucose absorption (Dieter 2005; Breuer 2003) while PPAR-? activator drugs (Kadowaki T 2002) such as rosiglitazone, pioglitazone are used to manage insulin resistance. GLP (Ajian, 2008) and DPP-4 (Inzucchi, 2002) inhibition have been added to the portfolio of diabetes management.

Diabetes market potential

Pharmaceuticals in Diabetes has a global market share of over US $850 billion and generally products are spread over insulin secretogogues, insulin, insulin sensitizers and for glucose utilization (Konno et al., 2001). These drugs cover the whole spectrum of disease conditions targeting organs from pancreas, liver, muscle and adipose. Along with the approved drugs there are also several nutritional supplements sold in different countries. In the US, the most popular herbal products are, Echinacea, Garlic, Goldenseal (Hydratis candensis), Ginseng, and Ginko (Hong et al., 2007).

Traditional Drugs

Traditional drug usage (Dwivedi & Dwivedi, 2007; Xu & Wang, 2002) for treatment of many diseases is known for centuries and they are captured in cultural folklore, Chinese Materia Medica and Indian Ayurveda. Out of the 1000 approved drugs, unaltered natural products account for 10% while derivatives of natural products form 29% and Synthetic drugs cover the remaining 61% of the total drugs. This analysis indicates the potential of natural products in human healthcare. Examples of drugs derived from natural sources are provided in the following Table 1:
Hypoglycemic activity of diterpenoids of the clerodane type (Farias et al., 1997) was compared to adebit and maninil and pharmacology of Diterpenes from Salvia species (Bonito et al., 2011) have been investigated. Phytochemical investigation on Globba pendula (Maulidiani et al., 2009) resulted in the isolation of a new naturally occurring 16-oxo-(8)-17-12-labdadien-15,11-olide and benzofuran-2-carboxaldehyde. Isoadrangapholidse was found to possess micromolar cytoprotective properties against various cancer cell lines MCF-7, PC-3, and H-460. Partial synthesis of the macrocyclic cembranoid diterpene providencin (White & Jana, 2009) comprising conjoined cyclobutane and furancarboxylate units has been published. The reported method makes use of deoxygenative ring contraction for the construction of tetrasubstituted cyclobutane. Tanshinone (Jung et al., 2009), was tested for tyrosine phosphorylation of the insulin receptor (IR) beta-subunit and as well as in 3T3-L1 adipocytes. In view of the tanshinones’s ability to effect translocation of GLUT-4 in the presence of insulin, these diterpenes could serve as leads for specific IR activators for diabetes. Stevia rebaudiana Bertoni (Huang et al., 2010), contains stevioside, rebaudioside A, B, C, D and E. Three steviol glycosides (Bitusta & Swati, 2011), stevioside, rebaudioside A and rebaudioside C were successfully isolated and purified from the extract of leaves of Stevia rebaudiana Bertoni by high-speed counter-current chromatography (HSCCC). Sapium insigne (ROYLE) BENTH. ex HOOK. fil, leaf extract gave rise to new phorbal derivatives (Devkota et al., 2009), 16-hydroxyphorbol-16-acetate and 4-beta-deoxy-16-hydroxyphorbol-16-acetae.

Improvement in extraction efficiency using liquid CO₂ has been resulted in extraction of Glycosides from Stevia rebaudiana Bertoni (Ercukcu et al., 2009). The major compound isolated was aurostoinulin. Aqueous extract of Clatia richardiana L., a traditional antidiabetic plant was found to be non-toxic which could be developed into an antidiabetic agent (Abourashed et al., 2003; Mossa et al., 1996). Scoparia dulcis Linn. aqueous extract was evaluated for its insulin stimulated glucose uptake (Beh et al., 2010) through the Glut-4 translocation components in L6 myotubes the results of which were compared to the action of insulin. Antioxidant potential assessed (Suresh et al., 2008) for medicinal plant species of Indian origin indicated that the presence of flavonoids, curcuminoinds, coumarins, and epicatechins could be responsible for the activity. Kaurenioic acid content in Wedelialaludosa (Acmena brasilensis) has been found to show variation depending on seasonal changes (Bresciani et al., 2004).

A new diterpene glycoside, amoxanthoside A (Kim et al., 2010) was isolated from Amomum xanthoides afforded and found to be cytotopic against four human cancer cell lines under in-vitro conditions. An aqueous extract (Latha et al., 2004) of Scoparia dulcis showed hypoglycemic action in streptozotocin induced diabetic rats. Biotransformation studies of steroidal compounds aimed at producing fragrant components has been published (Asakawa & Noma, 2010). Ayurveda describes Caesalpinia bonducella (Caesalpinia bonducella) for diabetes treatment and a compilation of available pharmacological data reveals the potential of the seeds for antihyperlipidemia. Trans-dehydrocrotonin (Silva et al., 2005) (t-DCTN), a major diterpene isolated from the Amazon medicinal plant Croton cajucara has been used as a medication for reducing glucose and lipid levels. An in vivo study revealed effects on cardiac and hypertension which could be attributed to nitric oxide release. Antidiabetic effects of trans-dehydrocrotonin (t-DCTN), from Croton cajucara showed hypoglycemic effect in alloxan-induced rats offering an option to evaluate the target interaction and benefit in diabetes (Silva et al., 2001). Investigation of galanin inhibition on insulin secretion in islets has been reported (Lindsberg & Ahren, 1991).

Andrographolide-lipoic acid conjugate has been evaluated for its potential role as a dual-functional (AL-1) (Ziajnik et al., 2009) agent that could act as hypoglycemic agent as well as protector of beta cells. Terpenoid, dehydroabietic acid (DAA) (Kang et al., 2009), suppressed TNFalpha (proinflammatory cytokines) while increasing adiponectin (an anti-inflammatory cytokine) levels, thereby improving the levels of plasma parameters in an otherwise poor situation in a diabetic condition. The results suggest that

### Table 1: Natural Product derived drugs:

<table>
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<tr>
<th>Disease</th>
<th>Original Drug</th>
<th>Modified Drug</th>
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<tbody>
<tr>
<td>Earliest antibiotics</td>
<td>Thienamycin (poor chemical stability)</td>
<td>Imipenem an analog.</td>
</tr>
<tr>
<td>Anticancer drug</td>
<td>Camptothecin (causes severe toxicity)</td>
<td>Topotecan and irinotecan</td>
</tr>
<tr>
<td>Marine pharmaceuticals</td>
<td>-</td>
<td>for ovarian and colon cancer</td>
</tr>
<tr>
<td>Anti-diabetic drug</td>
<td>Galegine(toxicity)</td>
<td>Metformin</td>
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</tbody>
</table>

From the drugs approved from 2005-2010 (Bhuvan & Vinod, 2011), 19 of them were Natural Product based and 36% of them are classified as NPs, 52% as semi-synthetic NPs and 10% as NP-derived drugs. Representative examples shown below cover diseases like diabetes, neuropathic pain management, breast cancer etc:

1. Exenatide (Byetta®-39 amino acid peptide from the oral secretions of Heloderma suspectum (Gila monster)-FDA 2009-Diabetes
4. Capsaicin (Quenzen®) isolated from chilli peppers FDA 2009 (a transdermal 8% patch for use in treatment of neuropathic pain combined with postherpetic neuralgia.

Thus natural products continue to be offering therapeutics as such and also form the basis for newer drugs although extensive and systematic investigations are warranted for bringing drugs from natural sources.

### Limitations of traditional drugs

Though natural products have beneficial effects for various ailments, they lack in good oral absorption, bioavailability (BA) and good pharmacokinetic properties (PK) and dynamic (PD) as exemplified by the fact that consumption of 8 g/day Curcumin is required for full efficacy owing to its very poor bioavailability (Benny & Antony, 2006; Antony et al., 2008; Baum et al., 2008). Similarly, Silymarin is insoluble, and has only 23-47% oral absorption due to poor bioavailability (Dixit et al., 2007). Strategies to overcome such poor bioavailability and solubility has been addressed through synergetic combination of natural products (Hetal et al., 2010), like piperine with Curcumin, popularly known as biocurcumin. Enteric coating (Fukuti et al., 2000), liposomal delivery (Robert, 2006) and nanoemulsion ( Mason et al., 2006) are other techniques used for enhancing biological properties of herbal drugs. Other techniques involve natural product derivatization (Guthikonda et al., 1987) such as functionalisation through insertion of Iodine in aromatic rings of natural products through N-iodosuccinimide under Lewis acid catalysis has been proposed as a tool for synthesis. Iodinated compounds provide access to several functional compounds by way of coupling, substitution reactions. Natural product structural modification (Zhou et al., 2010) has also been affected for the purpose of enhancing bioavailability and safety of the original compounds. Notable examples include conversion of Epicatechin to 3-O-acetyl and 3-O-alkyl derivatives which were tested for anticancer activity (Park et al., 2004), while 4-Hydroxyisoleucine derivatives (Catala et al., 2009) have been the subject of study for insulin secretion. Genistein derivatives (Rusin et al., 2009) have been investigated for anti-estrogenic activity while C-aryl substituted glycines have led to the new drugs (Xu et al., 2011) (FDA withheld approval for degapilfloxin (FDA panel, 2011) for SGLT-2 inhibition. The above list indicates that natural products provide a platform of structures that are specific to a set of targets while further tweaking of their structures might offer a structure activity relationship that would enable understand the activity, selectivity and toxicity of the basic skeleton present in the natural product.

DAA could serve as a supplement for obesity. Structure determination of the caged diterpenoid saudin (Mossaet.al., 1985) isolated in 1985, has been accomplished using X-ray crystallography (Boeckman et.al., 2002). Effects of Gingko biloba leaf extract on the learning and memory and expression of glial fibrillary acidic protein in hippocampal astrocytes of type 2 diabetic rats have been reported (Lin et.al., 2006). Isosteviol has been reported to improve insulin sensitivity in diabetic mouse models (Nordentoff et.al., 2008).

Bicyclic diterpenoids (Khushbaktova et.al., 1992; Roth et.al., 2002), salvin, salvicin and salviol, upon oral administration manifested hypoglycemic activity in rats, indicating their potential for preserving beta cells. Dolabellane Diterpenes (Morikawa et.al., 2004) isolated from nigella sativa showed ppar alpha agonist activity. Glucose stimulated Insulin secretion was observed with Rebaudioside A (Abudula et.al., 2004) and could serve a potential role as treatment in diabetes. Kaurane-type diterpene, 16a-H,17-isovaleryloxy-ent-kauran-19-oic acid, acanthioic acid and ent-kaur-16-en-19-oic acid inhibited PTP1B at sub micromolar concentrations (Na et.al., 2006; Lee & Wang, 2007) and structure activity relationships indicated that the presence of a hydroxy group or conversion of carboxyl group at C-19 in pimarane-type to alcohol reduced PTP1B inhibition. Antiulcer drug Geranylgeranylacetone (Hironori et.al., 2010) (GGA), induces HSP72 and gives rise to beneficial effect to obese animals arising out of mediated through HSP72 induction and JNK inactivation in the liver.

Derris indica roots extract gave rise to furanoflavonoids (Ranga et.al., 2009), which showed intestinal alpha-glucosidase inhibitory activity. Andrographolide demonstrated alpha-glucosidase and alpha-amylase inhibitory activity (Subramanian, et.al., 2008). Anti-cancer effect of carnosol in human prostate cancer PC3 cells (Johnson et.al., 2008) and its role in modulating multiple signaling pathways associated with carcinogenesis has been reported. Carnosol action could be mediated through targeting multiple signaling pathways including the AMPK pathway. Salacinol and kotalanol (Fig. 14) from roots of Salacia oblonga (Matsuda et.al., 1999) found showed alpha-glucosidase inhibitory activity, while Kotalagenin 16-acetate, inhibited aldose reductase through PTP1B. MeOH extract of the dried root of Salvia miltiorrhiza BUNGE (Labiatae) was found to exhibit significant inhibitory effect (Lee et.al., 2011). Abietane-type diterpene metabolites isotanshinone IIA, dihydroisotanshinone I, and isocryptotanshinone obtained through bioassay guided fractionation exerted non-competitive PTP1B inhibition (Han et.al., 2005). Carnosol (Lee et.al., 2011) has manifested a homeostasis effect in insulin deficient animals (Fig. 18). Maintenance of

### Table 2. Diterpenes, their anti-diabetic action and targets

<table>
<thead>
<tr>
<th>Actions and Targets</th>
<th>Structures</th>
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<tbody>
<tr>
<td>α-glucosidase inhibition</td>
<td><img src="image1" alt="Image" /></td>
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<tr>
<td>New kauranoids</td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td>Icetane diterpenes-Lupeol, Betulin</td>
<td><img src="image3" alt="Image" /></td>
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<tr>
<td>Spicatanol and spicatanol methyl ether</td>
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<tr>
<td>Furanoflavonoids</td>
<td><img src="image5" alt="Image" /></td>
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<tr>
<td>Andrographolide- A (alpha-glucosidase and alpha-amylase inhibitory activity)</td>
<td><img src="image6" alt="Image" /></td>
</tr>
<tr>
<td>Salacinol and kotalanol (Kotalagenin 16-acetate, inhibited aldose reductase through PTP1B)</td>
<td><img src="image7" alt="Image" /></td>
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glucose homeostasis upon chronic use of 1000 mg rebaudioside A has been observed in a trial (Maki et al., 2008).

Several new abietane (Lin et al., 2010) and new C(20)-norabietane diterpenes, together with known analogues, have been isolated from the stem bark of *Fraxinus sieboldiana*. Regulation of several pharmacological targets in Diabetic nephropathy by *Salvia miltiorrhiza* extracts has been reported (Lee et al., 2011). Hypoglycemic effect of a combination of stevioside with soy protein (Jeppesen et al., 2006) supplement has been reported and confirmation through long-term human study is needed. Preventive effects of a soy-based diet supplemented with stevioside on the development of the metabolic syndrome and type 2 diabetes in Zucker diabetic fatty rats (Dyrgskog et al., 2005). Controversy on the effect of Stevioside in enhancing basal insulin secretion has also been reported (Chen et al., 2006; Jeppesen et al., 2000; Chen et al., 2006). Intracellular signal transduction by Andrographolide 1 and 2 could be responsible for anti-diabetic nephropathy effect (Lee et al., 2010). Chemical conversion of natural Diterpene, lambertianic acid led to alkaloid-type compounds has been reported (Chernov et al., 2003).

PTP1B inhibition mediated by Amentoflavone, a biflavonoid from *Selaginella tamariscina* has been reported (Lee et al., 2008). Docking study has been performed with PTP 1B and the flavanoids and multiple pharmacophoric models have been proposed for the interaction of the flavanoids with the protein target. (-)-Hyrtiosa sesterterpenoid from the Okinawan marine sponge *Hyrtios erectus* was originally tested in vitro against KB cell for cytotoxic activity (Na et al., 2007), has been found to inhibit PTP 1B,owards treatment for diabetes (Chen et al., 2002). Extracts of roots of *Broussonetia papyrifera* was found to exert PTP1B inhibition (Lunardi et al., 2002).

Neuroprotection effects in human dopaminergic neuroblastoma cells by labdane diterpenes from *Fritillaria ebeiensis* has been evaluated (Xu et al., 2011).

Case histories of natural lead compounds in developing drugs, as exemplified by the third generation of antimalarial drug containing trioxane ring system inspired by the structure of artemisinin suggests that a careful analysis of
structural features of current drugs with natural compounds would be beneficial for the development of new drugs or leads. As discussed earlier, several diterpenes have been tested either in isolated pure form or extracts, for treating diabetes in cell based system or animal experiments.

The structures and activity information of the active diterpene ingredients are summarized in Table 2.

As can be seen from Table 2 above, the anti-diabetic action of Diterpenes are spread over α-glucosidase inhibition (icetexane diterpenes spicatanol and spicatanol methyl ether, Prabhakar RP 2009 & Aynampudi et.al., 2012) and activation of nuclear receptor ppar gamma (a Saurufuran A, a Furanoditerpene, Hwang BY et.al., 2002 & Carnosic acid and carnosol, Rau et.al., 2006). Reports on the use of in-silico methods for the evaluation of biological activity of Diterpenes are very few and known papers are not related to diabetes research as exemplified by the reports of neoclerodane diterpenes from 

Dolabellane Diterpenes from a common spice in India, nigella sativa, possesses anti diabetic activity through activating the ppar alpha (Morikawa 2004). Kaurane-type diterpene Rebaudioside A has manifested insulin secretion in preclinical studies in a extracellular Ca²⁺ dependant fashion (Abudula et.al., 2004). Carnosol has been found to intervene in several signaling pathways in cancer (Johnson et.al., 2008) and also in AMPK pathway which is targeted for glucose homeostasis indicating that it could be a potential anti-
The present review on Diterpenes indicates the anti-diabetic potential of these plant secondary metabolites and the requirement for a detailed investigation on ascertaining their mechanism of action. The structure and the reported activities of these rather neglected classes of natural compounds would kindle interest among pharmacologists and medicinal chemists in further elucidating the mechanism and development of an anti-diabetic compound. We have already initiated work on evaluating the interaction of selected Diterpenes with several diabetes targets employing in silico techniques. An understanding of type of receptor-ligand interaction with the respective diabetic targets and an analysis of their pharmacophoric model with the aid of the docking score would enable identification of structural skeleton of Diterpenes that would be necessary for imparting anti-diabetic activity. Through this, suitable modification of the structure of Diterpenes or a lead structure could be generated for medicinal chemistry efforts.

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