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EDITORIAL

Chemo-profiling of eucalyptus and study of its hypoglycemic potential

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Abstract

Constant escalations in the number of diabetics worldwide and the failure of conventional therapy to restore normoglycemia without adverse effects, in spite of tremendous strides in modern medicine, calls for naturopathy and alternative medicine. Because diabetes is multi-factorial and has secondary complications, prevention of hyperglycemia is the central dogma for its management. To date, no oral hypoglycemic exists which can achieve tight glycemic control without side effects. Dietary adjuncts, lifestyle interventions and a resurgence of interest in phyto-therapy have consequently gained ground. Natural hypoglycemics have attracted attention due to ease of incorporation in everyday diet, affordability, less adverse effects, and long term safety. Ethno botanical literature reports more than 800 anti-diabetic plants species. Eucalyptus is well represented in the Aboriginal Pharmacopoeias for its various pharmacological activities. Its hot aqueous decoction has been used as a hypoglycemic in various regions of world. This editorial attempts to summarize the data on the hypoglycemic potential of the different eucalyptus species, highlight the value of its natural biomolecules for the prophylaxis and treatment of type 2 diabetes, describe their mechanistic actions, shed light on the posology and safety aspects of eucalyptus and assess its applicability as a reinforcement to currently used therapy.

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Key words: Normoglycemia; Escalations; Eucalyptus; Central dogma; Dietary adjuncts; Aboriginal Pharmacopoeias; Natural biomolecules; Prophylaxis; Posology

Core tip: Eucalyptuses, indigenous to various countries of the world has been described in various Aboriginal, British and European Pharmacopoeias with its wide range of phytochemicals demonstrating a range of pharmacological effects including hypoglycemic action. The volatile and non-volatile constituents of Eucalyptus include terpenes and tri-terpenoids, flavonoids, flavanols, gallotannins, quercetin, euglobals, procyanidins, macro carpals. Pharmacopoeias have reported uses of hot eucalyptus leaf decoctions as tea to act as hypoglycemic agents. This editorial attempts to assess and highlight eucalyptus species with anti-diabetic potential and the probable biomolecules contributing to this along with their mechanistic role, as well as their posology and safety.

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INTRODUCTION

The world diabetic population is expected to show a steady growth of 366 million by 2030, despite the availability of insulin therapy and several synthetic hypoglycemics. Also, the severe side effects associated with the current treatment options cannot be neglected on a long-term basis[1,2]. Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia with

Table 1 Contrasting clinical and pathophysiologic features of types 1 and 2 diabetes

Features	Type 1 DM	Type 2 DM
Age at onset	Early, below 35 yr	Late, after 40-45 yr
Type of onset	Abrupt and severe	Gradual and insidious
Frequency of occurrence	10%-20%	80%-90%
Family history	Less than 20%	About 60%
Pathogenesis	Autoimmune destruction of β-cells	Insulin resistance, impaired insulin secretion
Body weight	Normal	Obese/non-obese
Genetic locus	Unknown	Chromosome 6
Condition of islet cells	Insulitis, β-cell destruction	No insulitis, later fibrosis of islets
Blood insulin level	Decreased insulin	Normal or increased insulin
Clinical management	Insulin and diet	Insulin, oral drugs, diet, exercise

DM: Diabetes mellitus.

disturbance of carbohydrate, protein or fat metabolism resulting from defects in insulin secretion, insulin action or both (World Health Organization, WHO, 1999). DM and the major complications associated with it such as retinopathy leading to blindness, diabetic foot ulcers necessitating limb amputations, neuropathy, nephropathy leading to end stage renal disease, is becoming the third greatest threat to the health of mankind after cancer, cerebrovascular and cardiovascular diseases. DM not only takes a heavy toll of lives around the world but imposes a serious financial burden on the sufferers and their family members. There are two main types of DM having contrasting clinical and pathophysiologic features; type 1 or insulin dependent diabetes mellitus (IDDM), and Type 2 or non-IDDM both (Table 1). Type 2 diabetes is found to be more prevalent, occurring mostly due to a combination of insulin resistance and inadequate compensatory insulin secretary response[3-6].

Pathophysiologically, type 2 DM, unlike type 1 DM, does not involve autoimmune destruction of pancreatic β-cells but involves multiple disturbances in glucose homeostasis including impaired insulin secretion, peripheral insulin resistance mostly in muscles, liver and adipocytes, and abnormalities in liver glucose uptake. The pancreas of type 2 diabetics produces insulin, yet insulin resistance prevents its proper use at the cellular level. Glucose cannot enter target cells and accumulates in the bloodstream, resulting in hyperglycemia. The high blood glucose levels often stimulate an increase in insulin production by the pancreas; thus, type 2 diabetic individuals often have excessive insulin production or hyperinsulinemia. Insulin is a potent anti-lipolytic hormone and restrains the release of free fatty acid (FFA) from the adipocytes by inhibiting the enzyme hormone sensitive lipase[6]. The fat cells of type 2 diabetics are markedly resistant to the inhibitory effect of insulin on lipolysis and, despite 2-4 fold increments in plasma insulin levels, the rate of lipolysis in post absorptive phase is still high. The availability of exogenous insulin to inhibit the elevated basal rate of lipolysis and to reduce the plasma FFA concentration is also markedly impaired. The pathogenicity is shown to be further aggravated by the circulating triglycerides which have been shown to impair insulin action in both liver and muscle. The glucose transport mechanism is severely impaired in the adipocytes and muscles of type 2 diabetics. Glucose transporter subtype 4 (GLUT4), mRNA and protein content are markedly reduced and the ability of insulin to elicit a normal translocation response and to activate the GLUT4 transporter after insertion into the cell membrane is decreased[3-6].

Although several synthetic hypoglycemics have been developed a safe and effective treatment paradigm is yet to be developed. Herbs are rich sources of bio-active compounds with versatile pharmacology and WHO has recommended traditional plant treatment for diabetes because of their safety, effectivity, availability and affordability. Moreover herbs can be used as dietary adjuvants. Hence there has been a great resurgence of interest in phyto-therapy with the NAPRALERT database (NAtural PRoducts ALERT) and the ethno-botanical literature reporting more than 800 anti-diabetic plant species[3-5,7,8]. Amongst these, this paper attempts to highlight the hypoglycemic potential of the different species of Eucalyptus. This is a diverse genus of flowering trees and shrubs, taxonomically from family Myrtaceae, indigenous to Australia, Tasmania and cultivated mostly in sub-tropical and warm temperate regions of the world. From ancient times the bark and leaves of different species of eucalyptus have been used as folk medicine for the treatment ailments such as cold, fever, toothache, diarrhea and snake bites. Popularly known as "gum tree", the use of eucalyptus as "herbal tea" has been recorded in Aboriginal, European and British Pharmacopoeias. Aqueous hot eucalyptus leaf decoctions have been used as a traditional remedy for DM[9]. Though there are over 500 species of eucalyptus this editorial will focus on four species viz. *Eucalyptus globulus* (*E. globules*) (Blue gum or Tasmanian blue gum), *Eucalyptus citriodora* (*E. citriodora*) (Lemon scented gum), *Eucalyptus camaldulensis* (*E. camaldulensis*) (River red gum or Murray red gum) and *Eucalyptus tereticornis* (*E. tereticornis*) (Forest red gum) with the chemo-profiling of their phyto-constituents, study of their mechanistic role as hypoglycemic agents and discussion of their status in alternative anti-diabetic therapy[9,10].

PHYTO-CHEMICAL PROFILING OF EUCALYPTUS

Eucalyptus contains both volatile and non-volatile fractions; amongst which the terpenoids are one of the major components comprising most of the essential oil of eucalyptus (eucalyptus oil), imparting its characteristic odor. The volatile, essential oils obtained by steam distillation comprise no less than 70% of 1,8-cineole, as reported by the pharmacopeias of Britain, France, United States, China *etc.*. Other volatile oil constituents include α-pinene,

Table 2 Phyto-chemicals and pharmacology of four eucalyptus species

Eucalyptus species	Major phyto-chemicals	Pharmacological actions
E. globulus (blue gum/tasmanian blue gum)	Euglobals, essential oils (1, 8 cineole, carvone, citral, citronellal, geranyl acetate, α-pinene, α-pinocarvone, β-pinene), hydrocarbons (4-hydroxytritriacontane-16, 18-dione, 16-hydroxy B tritriacontanone, n-Tritriacontane 16, 18-dione), Macrocarpals H, I, J	Anti-diabetic, anti-bacterial, anti-plaque, anti-tumor, anti-viral, anti-fungal, anti-histaminic, anti-inflammatory, anti-oxidant, anti-malarial
E. citriodora (temon scented gum)	Essential oils (cineole, citronellal, citronellic acid), sterols (9 β-sitosterol)	Anti-diabetic, analgesic, anti-fungal, anti-inflammatory, bone resorption inhibition, natural repellant
E. camaldulensis (river red gum/murray red gum)	Essential oil (aromandendrene, myrtenal, borneol, camphene, carvacrol, citronellal, citronellyl acetate, cryptone-α, terpenyl acetate), Flavonoids (apigenin, chrysin, flavone, luteolin, eriodictyol, hesperetin, naringenin, pinocem-brin), triterpenoids (oleanolic acid, maslinic acid, camaldulic acid, camaldulensic acid)	Anti-diabetic, anti-microbial, anti-nociceptive, anti-oxidative, cytotoxic
E. tereticornis (forest red gum)	Essential oils (1, 8-cineole, camphene, carvone, citral, citronellal, geranyl acetate, limonene, linalool oxide), phloroglucinol monoterpene derivatives (euglobal-T1, euglobal Ⅱc), urosolic acid, triterpene esters (tereticornate A and B)	Anti-diabetic, hepatoprotective, myorelaxant

E. globules: *Eucalyptus globules*; *E. citriodora*: *Eucalyptus citriodora*; *E. camaldulensis*: *Eucalyptus camaldulensis*; *E. tereticornis*: *Eucalyptus tereticornis*.

p-cymene, γ-terpinene. Terpenes like bicyclogermacrene, β-phellandrene are also reported. The chief constituents of the essential oil of *E. globulus* include: 1,8-cineole/eucalyptol (above 72%), α-terpineol, terpinen-4-ol, linalool, α-pinene, β-pinene, globulol, epiglobulol[10-12]. Citronellal, is the major component of the essential oil of *E. citriodora*, the other components being cis-geraniol, citronellol acetate, β-bisabolene, Dihydrocarveol acetate, 3-hexen-1-ol, Pregn-5-en-20-one,3,17-dihydroxy-3-acetate. The major components of the essential oil of *E. tereticornis* are: eucalyptol, 1R-α-pinene, isopinocarveol. The essential oil of includes *E. camaldulensis*: dihydrocarveol acetate, (-)-spathunelol, cis-nerolidol, megastigma-3, 7 (Z), 9-triene, thymol, aromadendrene, α-pinene, α-terpineol, drimenol, cubenol. Bioactives isolated from *E. camaldulensis* include pentacyclic triperpenoid, camaldulin along with ursolic acid lactone acetate and ursolic acid lactone; eucalyptanoic acid a triterpenoid acid; several flavonoid glycosides[10-14].

Non-volatile constituents like flavonoids, triterpenoids, and tannins have been isolated from various eucalyptus species. An important group of phenolic compounds of eucalyptus are the formylated phloroglucinols, notable amongst which are euglobals, macrocarpals, sideroxylonals, robustadials. These show a wide range of biological actions including anti-bacterial, antioxidant, anti-inflammatory, HIV-RTase inhibitory, anti-malarial and anti-tumor promoting activities[9-11,15,16]. Osawa and Namiki[17] reported the presence of strong antioxidants in the leaf wax of a range of eucalyptus species. 4-hydroxytritriacontane-16, 18 dione, a very powerful antioxidant, was isolated from the leaf wax of *E. globulus* by Osawa and Namiki[18] and makes up more than 0.3% of the leaf wax content. *E. globulus* could serve as an abundant source of powerful antioxidants. Phenolics including tannins, flavonol glycosides, acylated flavonol glycosides have been isolated from the species *E. camaldulensis*. Five bioactive compounds, macrocarpals A-E, detected in the ethanol extracts of the leaves of *E. globulus* showed HIV-RTase inhibitory activity[9-11]. Along with their antibacterial actions, macrocarpals A, B, C, D in the concentration range of 2-2.8 μmol have been shown to inhibit aldose reductase, the target enzyme in the control of diabetic complications[9,10,18-21]. Euglobals are cyclo-adducts of formyl phloroglucinol. Euglobal-Ⅲ was first isolated from buds of *E. globulus* and the presence of Euglobal-T1 has been reported in *E. tereticornis*. Twelve euglobals isolated from the leaves of *E. globulus* showed stronger anti-inflammatory potential than indomethacin and similar inhibitory effects to berberine. Flavonols (quercetin, myricetin, kaempferol), proanthocyanidins, anthocyanins have been isolated from leaves of the eucalyptus species[9-13,15,16,18-20].

Cumulative details of the active phyto-constituents of the four eucalyptus species are provided in Table 2.

One important therapeutic intervention in the treatment of diabetes the reduction of post-prandial hyperglycemia by inhibiting the actions of carbohydrate hydrolyzing enzymes like α-amylase and α-glucosidase. Several biomolecules of the phyto-kingdom have been found to be potent α-amylase and α-glucosidase inhibitors[22-25]. Amongst the major components isolated from the eucalyptus species under study the flavonoids, (mostly quercetin, kaempferol, myricetin), phenolics (including tannins, ellagic acid, gallic acid), and terpinoids (including ursolic acid, oleanolic acid, p-cymene, 1, 8-cineole, 1-(S)-α-pinene) are found to exhibit strong α-amylase activity while polyphenols, proanthocyanidins, anthocyanins are found to be potent natural α-glucosidase inhibitors. Other enzymes such as dipeptidyl peptidase 4 (DPP4), aldose reductase (AR), angiotensin converting enzyme (ACE), and peroxisome proliferator activated receptor (PPAR)-γ also play significant roles in diabetes[16]. AR, a member of the aldo-keto-reductase super family, is the first and rate limiting enzyme in the polyol pathway and reduces glucose to sorbitol, utilizing NADPH as a cofactor. Sorbitol is then metabolized to fructose by sorbitol dehydrogenase. In DM, due to increased availability of glucose in insulin in-sensitive tissues such as lens, nerves, retina there is increased formation of sorbitol through the polyol pathway. Intracellular accumulation of sor-

bitol is implicated in chronic complications of diabetes including cataract, retinopathy and neuropathy. AR-inhibitors prevent the conversion of glucose to sorbitol and are able to control diabetic complications[16]. Limited literature data have shown that natural biomolecules with potent aldose reductase inhibitory actions are: flavonoids like Quercetin, Quercitrin, Myricitrin, coumarins, monoterpenes, stilbenes *etc.*[16,26]. Molecular docking analyses have shown that the binding energies of phyto-chemicals like myrcene, citral, geraniol (-8.76, -7.24 and -7.93 kcal/mol respectively) are sufficient to inhibit the activity of aldose reductase[27]. Results of *in-silico* docking studies have shown that flavonoids with binding energy ranging between -9.33 kcal/mol to -7.23 kcal/mol contributed to AR inhibitory properties[28]. The four species of eucalyptus chosen for study of hypoglycemic potential to contain a number of flavonoids and monoterpenes and AR inhibition may be one of the possible modes for the hypoglycemic actions of eucalyptus[16,26].

Increase in the level of reactive oxygen species (ROS) is another pathogenic factor in type 2 diabetes. Attenuation in ROS level may be due to increased production/diminished depletion by enzymic catalase, glutathione peroxidase, and superoxide dismutase antioxidants. Natural antioxidants which scavenge free radicals may be acting synergistically with their hypoglycemic activity in exerting an overall anti-diabetic action. The presence of powerful antioxidant compounds in *E. globulus* contributes significantly to its hypoglycemic potential[16,18-20].

PPAR-γ is a key receptor in lipid and glucose homeostasis because of its ability to reduce the plasma FFA. Phyto molecules can exert their insulin sensitizing actions through their high affinity for the receptor PPAR-γ and hence can act as therapeutic targets for type 2 diabetes. Terpinoids are found to act as PPAR modulators regulating carbohydrate and lipid metabolism and are hence a promising therapeutic target for type 2 diabetes. Chemo-profiling of the eucalyptus species under study depicted the presence of several terpenoids and PPAR antagonism may also be a possible mode for the hypoglycemic action of eucalyptus[29]. ACE is an important enzyme involved in vascular tension and is hence associated with hypertension, a long term complication of diabetes. Along with oxidative stress, ACE plays a key role in diabetes. ACE activates histidyl leucine dipeptide (Angiotensin- Ⅰ) into the potent vasoconstrictor Angiotensin- Ⅱ. Angiotensin- Ⅱ influences the release of aldosterone, which increases blood pressure by promoting sodium retention in distal tubules. Thus, biomolecules with ACE inhibitory activities can be considered as useful therapeutic targets against diabetes, as evidenced by United Kingdom Prospective Diabetes Study study[30]. Natural biomolecules like flavonoids, flavonols, anthocyanins, tri-terpenes are found to be potent ACE inhibitors, and find use in controlling hypertension, one of the problems associated with DM. Molecular docking studies also indicate the use of herbal ACE inhibitors in the management of DM[31].

Glucagon-like peptide-1 (GLP-1) is a remarkable anti-diabetic gut hormone with its combined actions of stimulating insulin secretion, increasing beta cell mass, inhibiting glucagon secretion, reducing the rate of gastric emptying and inducing satiety. GLP-1 is rapidly deactivated by DPP4 and animal studies have shown that inhibition of DPP4 improves glucose tolerance and increases insulin secretion. Thus, natural biomolecules with DPP4 inhibitory activity will help to increase the levels of endogenous GLP-1 activity and act as an important therapeutic bullet against type 2diabetes. Molecular docking studies have suggested the use of herbal DPP4-inhibitors as a therapeutic target against diabetes and suggest that tri-terpenoids, steroids and phenolic constituents are mainly responsible for the activity[32].

HYPOGLYCEMIC POTENTIAL OF EUCALYPTUS

Although the eucalyptus species exhibits various pharmacological actions (Table 2) the central focus of this editorial is on the hypoglycemic potential of eucalyptus. *E. globulus* is used in the traditional treatment of diabetes. In STZ-induced diabetic mice, incorporation of *E. globulus* in diet (62.5 g/kg) and drinking water (2.5 g/L) reduced the hyperglycemia and associated weight loss. Gray *et al*[33], suggested that an aqueous extract of *E. globulus* (0.5 g/L) enhanced 2-deoxy-glucose transport by 50%, glucose oxidation by 60%, and incorporation of glucose into glycogen by 90% in abdominal muscle of mice and a 20 min incubation of the same extract (0.25-0.5 g/L) evoked a step-wise, 70%-160% enhancement of insulin secretion from the clonal pancreatic beta-cell line. In 2009 Basak *et al*[34], studied the anti-diabetic actions of the essential oil of *E. camaldulensis* and found that it inhibited both α-amylase and α-glucosidase in a non-competitive manner and also exhibited greater antioxidant potential than butylated hydroxyl toluene and curcumin, giving further evidence in support of its hypoglycemic actions. Nakhaee *et al*[35] evaluated the effects of *E. globulus* (20 g/kg in diet and 2.5 g/L in drinking water) on lipid peroxidation, protein oxidation and antioxidant power in plasma and liver homogenate as well as glycated hemoglobin. They suggested that *E. globulus* possess antidiabetic and antioxidant property, reduces oxidative stress mostly by reducing the plasma glucose level in diabetic rats, thereby preventing excessive production of free radicals through glycation of the proteins. Patra *et al*[36], studying the effect of aqueous leaf extract (150 mg/kg body wt) on blood gluco-lipid profile in alloxan-induced diabetic rats, showed that *E. globulus* possess hypoglycemic activities with concurrent hypolipidemic effects. They reported that the decrease in blood gluco-lipid profile caused by the aqueous extract of *E. globulus* at a dose 150 mg/kg body wt, is comparable with the effect of sulphonylureas which promote insulin secretion by closure of K^+ ATPase channels, membrane depolarization and stimulation of Ca^{2+} ion

influx, an initial key step in insulin secretion. The ability of *E. globulus* to restore body wt in alloxan treated diabetic rats may be due to its hypoglycemic effect while the hypolipidemic effect is due to inhibition of endogenous synthesis of lipids. In alloxan-induced diabetic models, because of metabolic aberration there is a high turnover of triglycerides and phospholipids. *E. globulus* is thought to antagonize this metabolic aberration and restore normal metabolism by tilting the balance from high lipid to high carbohydrate metabolism in alloxan diabetic rats. Patra *et al*[36] showed the antidiabetic activity of the aqueous extract of *E. citriodora* leaf in alloxan-induced diabetic rats. Aqueous extract of leaves of *E. citriodora* exhibited significant antidiabetic activity which was comparable with the standard drug Glibenclamide. Villaseñor *et al*[37] ,using an oral glucose tolerance test, showed that *E. tereticornis* exhibits hypoglycemic activity in mice at a dose of 5 mg/20 mg. Experiments carried out by Shahraki *et al*[38] showed that eucalyptus aqueous extract decreased blood glucose level but increased liver enzyme activities in STZ-induced diabetic male rats. The probable hypoglycemic effect may be due to water soluble compounds present in the aqueous extract of eucalyptus which effected on glucose metabolism in fat or skeletal muscle cells and decreased blood sugar by increasing the glucose influx in the cells. Moreover, effects on glycolysis and an increase in glucose consumption in fat and skeletal muscles are also suggested to cause a decrease in blood glucose. Gallagher *et al*[39] investigated the effects of administration of eucalyptus extract on intestinal absorption in rat cultured cells where the extract decreased glucose in the culture environment and increased glucose uptake by the cells. Sugimoto *et al*[40] have shown that *E. globulus* leaf extract (10 g/kg diet) inhibited intestinal fructose absorption and suppressed adiposity due to dietary sucrose in rats. The *E. globulus* leaf extract inhibited intestinal fructose absorption in a dose dependent manner and simultaneously reduced plasma and hepatic triacylglycerol concentrations. The suggested mechanism is that fructose is transported across the intestinal brush border membrane by the specific transporter GLUT5 and inhibiting intestinal fructose absorption prevents adiposity in subjects consuming large amounts of sucrose and fructose. Fructose is metabolized in the liver by fructokinase which is later split by the action of aldolase B into glyceraldehydes and dihydroxyacetone phosphate, the intermediates of glycolytic sequence. Fructose can provide carbon atoms for both glycerol and acyl portions of the TG molecules and is considered to be more lipogenic than glucose. *E. globulus* leaf extract is found to inhibit the activities of fructokinase and G6PDH, preventing the activation of fructose metabolism and fatty acid synthesis induced by dietary sucrose. *E. globulus* leaf extract simultaneously inhibits intestinal fructose and sucrose absorption and shows enough potential to be used as a natural food additive in fructose/sucrose rich junk foods[40,41]. Gireesh *et al*[42] showed that incorporation of *E. globulus* in the diet (20 and 62.5 g/kg) and drinking water (2.5 g/L aqueous extract) of STZ-induced male wistar rats ameliorated their diabetic state in a dose dependent manner with partial restoration of pancreatic β-cells and repair of STZ-induced damage. Thus, this study supports the use of *E. globulus* as an effective antihyperglycemic dietary supplement which can, in a dose dependent manner, compensate for STZ-induced cell damage of pancreatic β-cells[42]. Studies carried out by Pérez *et al*[43] showed that oral and *ip* administration of eucalyptus extract (25, 50, 75, 100 g per 250 mL water) in alloxan-induced diabetic mice led to hypoglycemia up to 36% (oral) and 25% (*ip*), respectively. Ahlem *et al*[44] showed significant reduction in blood glucose in alloxan-induced diabetic rats with *E. globulus* extract (130 mg/kg body wt) but, since liver glycogen level was not restored, did not recommend the insulin stimulatory effect of eucalyptus, rather highlighting the antioxidative potential of *E. globulus*.

TOXICOLOGY AND POSOLOGY OF EUCALYPTUS

Limited research data are available on the posology and toxicology of eucalyptus. Shalaby *et al*[45] reported that the essential oil from *E. globulus* in its undiluted form showed an LD_{50} value (median lethal dose) of 2334.4 mg/kg body wt and considered it to be moderately hazardous as per WHO specifications. The European Medicines Agency Assessment Report, 2012 on *E. globulus* gave some clinical and non-clinical data on the posology and toxicology of eucalyptus. Other than the traditional use of eucalyptus leaf decoction as herbal tea there is no such specific medicinal product mentioned in any pharmaceutical market overview using eucalyptus leaf or preparation as a single active ingredient. However there are herbal preparations in the literature and monographs on the use of dried leaf infusion or hot infusion mostly as an inhalant, herbal tea, powdered whole drug and aqueous alcoholic extracts or tinctures of varying strengths, or as one of the ingredient of polyherbal preparations mostly for the treatment of cough associated with cold[46]. Aboriginal Pharmacopoeias and other earlier citations have recommended use of eucalyptus in treating fever, neuralgic pain, asthma, lung tuberculosis, UTIs, antisepsis, rheumatism, malaria, fevered diarrhea, gum bleeding, anti-helminthic, wound, acne, poorly healing ulcers, gonorrhoea[7,47]. Available data on the posology of eucalyptus is highly variable and inconsistent. Nonetheless, according to the European monographs, British Herbal Compendium, German Pharmacoepia, Spanish literature and literature citations a dosage regimen is described for infusions of from 1.5-3 g of herbal substance for single use and 2.5-20 g for daily use. Posology given by Pharmacopee Francaise recommends use of herbal tea prepared with 1.5-3 g of eucalyptus leaves in 150 mL of boiling water, steeping time 10-15 min, 4 times a day. For inhalations the posology ranges from 2-3 g per single dose taken up to 3 times a day. For

the oral use of tinctures the posology data widely varies from 1-10 g a day, however the most cited data suggest 2.5 g tincture 1-3 times a day which corresponds to 0.5 g herbal substance as a single dose and 0.5-1.5 g herbal substance a day[47].

Similarly, toxicological data on the eucalyptus are scarce and most reports are on 1,8-cineole which is the main constituent of the essential oil of the eucalyptus species. Hagan *et al*[46] reported the LD_{50} oral dose to be 2480 mg/kg body wt; De Vincenzi *et al*[48] reported it to be 2400 mg/kg per day, although encapsulated cineole showed a dose-related histopathological alteration in liver, kidney and parotid gland at a maximal dose of 5607 mg/kg per day. Kristiansen *et al*[49] found that administration of 1,8-cineole at doses 500 and 1000 mg per day for 28 d caused renal lesions in Wister rats. In any case, use of concentrated extract or undiluted oil is not recommended. Pharmacokinetically, 1,8-cineole is very well absorbed orally, topically, or via mucosa and reaches a peak plasma concentration within 1-3 h and is subject to renal and pulmonary excretion. The Commission E monograph cites a number of side effects of eucalyptus following oral administration including allergic skin reaction, shock, tremor, ataxia, aphasia, vomiting, dizziness, urticaria, diarrhea, epigastric pain, and topical reactions such as pustular rash. Co-administration is to be avoided with barbiturates, benzodiazepines, anti-depressants. The side effects can be severe with a number of contraindications so use during pregnancy and lactation is best to be either avoided or only under strict medical supervision since insufficient safety data is available on humans[46].

CONCLUSION

The detailed chemo-profiling and available literature on the species of eucalyptus discussed in the manuscript, supports their hypoglycemic potential and shows that there is enough promise to use eucalyptus or its bioactive phytomolecules as important therapeutic target against type 2 DM. Species presenting a wide range of phyto-chemicals need further screening using the latest combinatorial/bioinformatic/computational approaches aided by the latest analytical methodologies which apply hyphenated techniques to the search for novel lead compounds and the mechanistic study of their hypoglycemic potential. However, despite immense potential the popularity of herbal medicines is always hindered due to the traditional ways in which they are delivered, which in many cases not only causes patient non-compliance but also results in reduced efficacy of the drug due to bioavailability problems, organoleptic unacceptability etc. Keeping in mind the hypoglycemic potential of eucalyptus, efforts are needed to develop definitive dosage formulations with eucalyptus bio-actives. Nano-technical approaches can be exploited for their delivery so as to minimize the side effects, bioavailability and organoleptic problems associated with them and, thereby, increase the popularity of using eucalyptus against type 2 DM.

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