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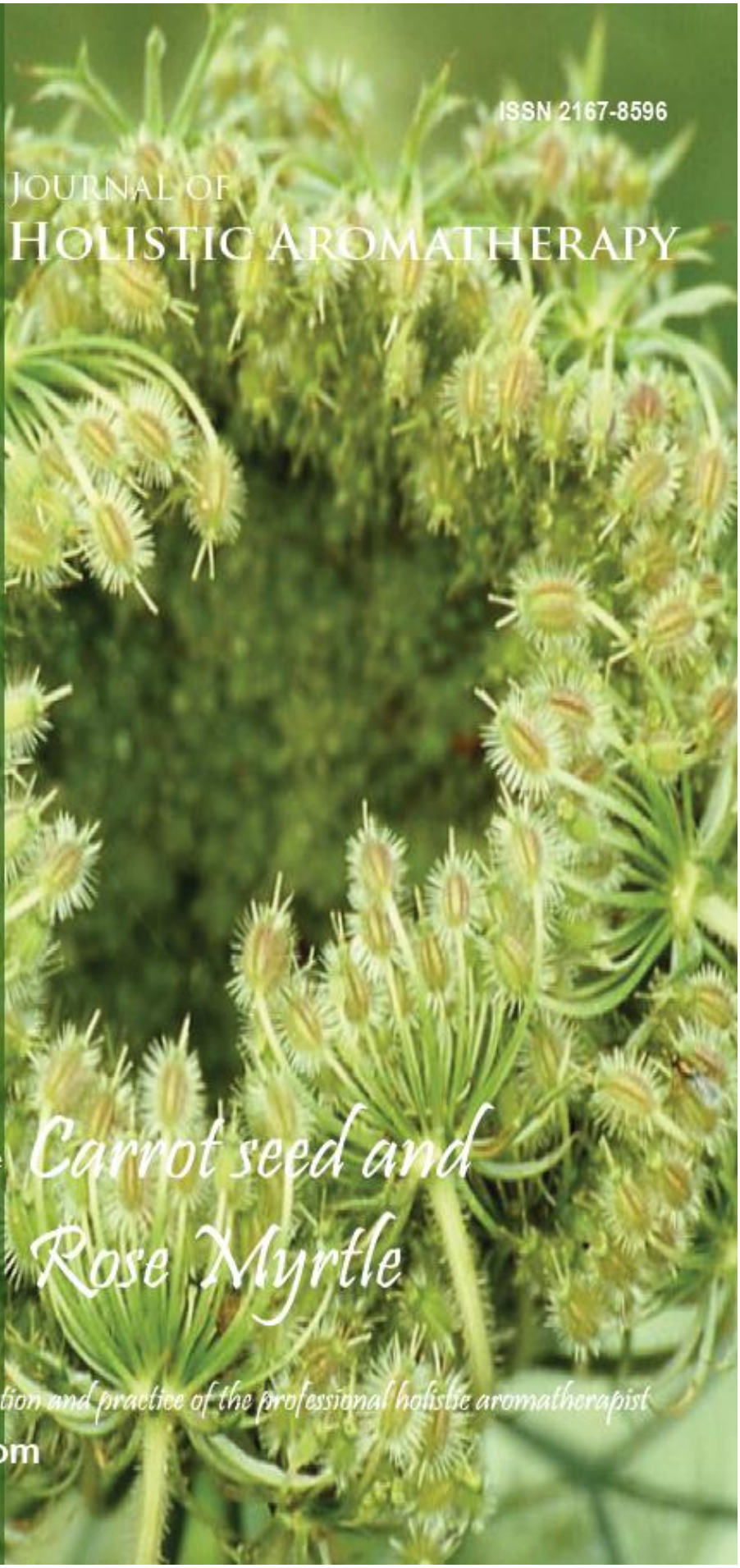

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Potential Use of Essential Oils in Prevention and Management of *Diabetes Mellitus*

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Introduction

The first cases of a disease with unusual symptoms causing the patient to urinate frequently and lose weight rapidly, accompanied by a noticeable sweetness of urine and blood, were described by ancient Egyptians around 3000 years ago. The term *diabetes* was first used by Aretaeus of Cappadocia (81–133AD). Later, in the 19th century it was discovered that the liver and pancreas play a crucial role in glycogenesis, and it was proposed that diabetes is due to excess glucose production. The hormone insulin was first isolated by Banting and Best in 1921 and the importance of this work was recognised with a Nobel Prize.

Diabetes mellitus, which is a result of hyperglycemia developed due to insufficient insulin action (defects in insulin secretion and/or insulin action), has been linked to genetic defects (of the β-cells and in insulin action) (Naylor et al, 2011), anatomical defects and/or pathology (diseases of the exocrine pancreas, endocrinopathies) and environmental factors (drug overdoses, toxic chemicals), and can lead to a variety of glucose metabolism disorders. Diabetes is classified in four basic groups: type 1 *Diabetes mellitus* (immune-mediated/autoimmune diabetes, idiopathic diabetes and fulminant, associated with viral infection and/or pregnancy); type 2 *Diabetes mellitus*; *Diabetes mellitus* due to other specific mechanisms; and gestational *Diabetes mellitus*. Type 1 and type 2 diabetes cause serious health conditions including peripheral neuropathy, autonomic neuropathy, auditory neuropathy, brain inflammation with following elevation of dementia (Samaras et al, 2014), optic atrophy and loss of vision, change of carbohydrate and protein metabolism (Pareek et al, 2009), hypertension, change of lipoprotein metabolism, depression (Holt et al, 2014), obesity, pancreatic islet β-cells destruction, post-diabetic candidiasis and periodontal disease (Negrato et al, 2012), protein metabolism disturbances, kidney failure, and others.

According to the National Diabetes Statistics Report (CDC, 2014), in 2011 in the USA, a total of 228,924 people of all ages had kidney failure due to diabetes. Diabetic patients are known to be more susceptible to various types of infection, skin diseases and systemic inflammations. Diabetes is also associated with increased risk of different types of cancer, such as liver, pancreatic, endometrial, colorectal, breast, and bladder cancer (Li, 2012). It was also suggested that development of diabetes could be associated with enterovirus infection (Craig et al, 2009). The main factors involved in rapid development of diabetes could be: increased level of lipid peroxidation, impaired glutathione metabolism and level of antioxidant enzymes, production of free radicals, and increase in advanced glycation products.

The number of diabetic cases has surged dramatically in the last 10–15 years. According to the World Health Organization (WHO), the number of cases of *Diabetes mellitus* between 2000 and 2030 is expected to double (from 171 to 366 million and more). Type 2 *Diabetes mellitus* is a major cause of cardiovascular problems in the United States (Lloyd-Jones et al, 2009). The economic losses, low quality of life and mortality rate caused by this epidemic are huge, and new approaches to treatment and prevention, as well as well-planned global initiatives which can help to combat the problem, are urgently required.

Essential oils and diabetes

Essential oils have been used since ancient times to

improve quality of life in general and ease stress and promote relaxation. They have been used in many ways, from soothing insomnia and depression to improving skin integrity, healing wounds, and combating infection. Essential oils can be successfully used in the management of diabetes, hypertension and systemic inflammation (Politeo et al, 2006).

Hyperglycaemia, which is the main symptom of *Diabetes mellitus,* causes lipid peroxidation and cell membrane damage, and plays a role in the development of complications such as cataracts, nephropathy, and neuropathy. Antioxidants can protect cells by inhibiting the peroxidation chain reaction, and a variety of essential oils are loaded with compounds with powerful antioxidant properties, such as α-pinene, limonene, carvacrol, thymol, linalool, eucalyptol, β-citronellol and nerolidol (Ruberto and Baratta, 2000; Saleh et al, 2010).

Essential oils can be used to reduce the side effects of some of the complications of diabetes, can suppress inflammatory processes, and can potentially counteract metabolic changes caused by diabetes through activation of the nuclear Peroxisome proliferator-activated receptors (PPARs)(Weidner et al, 2013). Specific essential oils are used to prevent diabetes and manage diabetes-related conditions by producing the hypoglycemic effect by stimulating insulin secretion from cells of pancreatic islets via potentiation of glucose-induced insulin release or increased peripheral uptake of glucose.

It has been demonstrated that the essential oil of Rose Geranium (*Pelargonium graveolens* var. *roseum*), Eucalyptus (*Eucalyptus globulus*), Lemongrass (*Cymbopogon citratus*) and others such as Coriander (*Coriandrum sativum*), Lavender (*Lavandula angustifolia*), Ylang Ylang (*Cananga odorata*), Marjoram (*Origanum majorana*), Bergamot (*Citrus aurantium* var. *bergamia*), as well as their aromatic constituents (including geraniol, *d*-limonene, camphene, citral, linalool, β-myrcene and others) demonstrate powerful anti-inflammatory, antioxidant and potential anti-diabetic properties. However, there are essential oils and herbal extracts that should never be used by diabetics in any form, such as Angelica (*Angelica archangelica* and *Angelica synensis*) which contains a variety of polysaccharides including glucose, fructose, galactose, arabinose, rhamnose and xylose (Chao and Lin, 2011).

Rose Geranium essential oil

Scented Geranium leaf
E.Ackermann/Flickr CC

The essential oil of Rose Geranium is distilled from plants native to South Africa, Zimbabwe and Mozambique, and cultivated in Europe, Asia and North America with limited production in Algeria, China, Reunion Islands, Morocco, Egypt, Madagascar, and Spain. It is demonstrated that water distillation of the Rose Geranium plant produces a higher oil yield (0.16–0.22%) in comparison with water–steam distillation (0.09–0.12%) and steam distillation (0.06–0.18%) (Babu and Kaul, 2005).

Rose Geranium essential oil contains a high percentage of oxygenated monoterpenes (up to 76.85%), and lesser amounts of monoterpene hydrocarbons (average, 1.13%), oxygenated sesquiterpenes (average, 3.31%) and sesquiterpene hydrocarbons (average, 2.16%) (Boukhatem et al, 2013). According to gas chromatography/mass spectrometry (GC/MS) analysis, Rose Geranium essential oil has 20–47 compounds which vary depending on season, weather and soil conditions, including: β-citronellol (16–32%), geraniol (10–25%), δ-selinene (6–10%), citronellyl formate (5–12%), geranyl formate (6–15%), linalool-l (3–5%), geranyl butyrate (1.2–3%), and geranyl acetate (0.5–2%). This ratio between essential oil compounds varies depending on extraction techniques used (steam distillation, solvent extraction, supercritical CO_2 extraction). Rose Geranium essential oil has been used for many years in traditional medicine as antiasthmatic, anti-diabetic, antidiarrhoeic, antihepatotoxic, anti-inflammatory, antioxidant, and diuretic. Geranium and Rose Geranium essential oil reduces oxidative stress by preventing the generation of free radicals and inhibiting the development of diabetes and demonstrates exceptional anti-inflammatory properties (Boukhris et al, 2012; Boukhatem et al, 2013). One of the main compounds of Rose Geranium essential oil—geraniol (acyclic monoterpene alcohol) which is known for potent anti-inflammatory properties—was found to ameliorate fructose-induced obesity, hyperglycemia, hypertension and hyperuricemia, and improve insulin sensitivity. According to studies, geraniol modulates the adipokines to reduce inflammation, and inhibits prostaglandin E2, tumor necrosis factor (TNF)-α and HMG-CoA reductase (Ibrahim et al, 2015).

Eucalyptus essential oil (*Eucalyptus* spp.)

From ancient time, leaves and bark of different types of Eucalyptus, known as a "gum tree," were intensively used for soothing cough and combating cold, fever, toothache, and other pathological conditions in Britain, France, the United States and China. Distilled from leaves and twigs of the trees and shrubs, Eucalyptus essential oil is a great source of volatile essential oil and phenolic compounds including tannins, glycosides, flavonols and glycosides isolated from the species, and demonstrates powerful anti-oxidant, anti-bacterial, anti-inflammatory, anti-malarial and anti-tumor properties. Eucalyptus essential oil contains oxygenated and hydrocarbon monoterpenes (46.5% and 23.37% of the oil, respectively), aromatic compounds (17.44%), and hydrocarbon and oxygenated sesquiterpenes (11.46% and 1.23%, respectively). A variety of Eucalyptus essential oil may contain at least 4% to as high as 90% 1,8-cineole. Other constituents quantified in Eucalyptus essential oil are: tepinen-4-ol (up to 23.46%), γ-terpinene (up to 17.01%), *para*-cymene (8.10–16.70%), piperitone (5.90%), methane-1,2,3-triol (4.41%), α-pinene (4.16–9.22%), pinanediol (4.07%), cis-sabinol (3.11%), globulol (2.52%), eudesmol (2.38%), α and ß-phellandrene (2.20–5.13%), α-selinene (0.57%) and cycloprop(e)azulene (1.23–5.66%). Eucalyptus essential oil, as well as some of its main constituents, has demonstrated antioxidant activities and its water extract reduces oxidative stress by reducing the plasma glucose level in diabetic rats, thereby preventing overproduction of free radicals through glycation of the proteins (Patra et al, 2009). The hypoglycemic effect may be explained by decreased blood sugar by increasing the glucose influx in the cells in type-2 experimental diabetes.

Eucalyptus species
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The lysosomal enzymes, which are involved in damage to connective tissue due to genetic defects in their expression or escape into extralysosomal medium, contribute to several human diseases, including diabetes, and always are mediators of chronic inflammatory disease (Ravichandran et al, 1990). Stabilization of the lysosomes by compounds of the Eucalyptus essential oil has a beneficial effect on the lysosomal membrane permeability in various hepatic disorders and type-2 diabetes involving abnormal fragility of the lysosomes.

Eucalyptus essential oil demonstrates antifungal and antimicrobial properties, and a powerful inhibitory effect on the growth of Candida albicans in both normal and diabetic rats (Schelz et al, 2006; Gray and Flatt, 1998). 1,8-Cineole(eucalyptol) is a monoterpene oxide present in the Eucalyptus essential oil and is widely used to treat respiratory diseases aggravated by infection and low immune system response, and also demonstrates an anti-inflammatory effect with possible preventive action for gastrointestinal inflammation and diabetic ulceration.

It is important to remember in spite of low toxicity, taken orally by adults in doses over 0.06 to 0.2 ml, Eucalyptus essential oil can cause multiple allergic reactions, vomiting, aphasia, ataxia, diarrhea, dizziness, stomach pain, tremor, tachycardia and weak irregular pulse, nephritis, miosis and mydriasis, which could be a result of liver, kidney and spleen toxicity, and even death (Hu et al, 2014; Patel and Wiggins, 1980; Gurr and Scroggie, 1965; Tibballs, 1995, Webb and Pitt, 1993). Topical exposure may cause redness, irritation and burning sensation, pruritus and rash (Spoerke et al, 1989). It is important to use Eucalyptus essential oil in proper dosage, duration and method bearing in mind any drug/essential oil interaction. *Eucalyptus globulus*, *E. radiata* and *E. smithii* essential oils should not be used on or near the face of infants or children under the age of 10. People with dermatitis are advised to use no more than one drop of *Eucalyptus globulus*, *E. radiata* and *E. smithii* essential oils per 5 ml of a carrier oil or lotion for topical application, because of the 1,8-cineole content (Purchon and Cantele, 2014; Tisserand and Young, 2014).

Eucalyptus oils and extracts should not be administered with anti-depressants, barbiturates and benzodiazepines. It should not be used during the pregnancy and lactation.

Lemongrass essential oil (*Cymbopogon citratus*)

Distilled and exported from the Philippines, the first sample Lemongrass essential oil was displayed at the World's Fair at London's Crystal Palace in 1951. Originally from Sri Lanka and South India (known locally as "choomana poolu"), it is now widely cultivated in the tropical areas of America and Asia. Lemongrass essential oil and herb extracts are intensively used as a flavoring agent and in folk medicine as an analgesic, anticonvulsant, antiemetic, antigout, anti-

hepatotoxic, antimalarial, anti-protozoan, antispasmodic, antitussive, antirheumatic, antiseptic, diuretic, febrifuge, fungicidal, hypotensive, stimulant (central nervous system and management of gastrointestinal disorders), and obesity. The anti-inflammatory, anti-oxidant, and cytoprotective activity of Lemongrass essential oil is well documented (Cheel et al, 2005). Lemongrass essential oil protects DNA against environmental damage and exhibits anticarcinogenic properties as well (Bidinotto et al, 2010).

Lemongrass essential oil consists of mainly 48 constituents with varying percentages depending on season, weather and soil conditions. These include: citral (65–85%) (which is a combination of geranial (37.58–48%) and neral (25–42%)), citronellal (appx. 24%), citronellol (appx. 18%), β-myrcene (3.18–8%), nerol (3.14–4.5%), 3-undecyne (1.46–3.5%), and geranyl acetate (10.6–3%). As a moderate inhibitor of mammalian α-amylase, citral demonstrates lowering of blood glucose, alongside with normalization of blood lipid profile, promoting weight loss and decreasing food intake in experimental diabetic rats *in vivo*. The citronellal and citral play detoxification and anti-cancer roles by inducing glutathione-S-transferase (GST) activity. In studies, Lemongrass essential oil significantly improved the number and β-cell mass in pancreatic islets which would increase the secretion of insulin, followed by the peripheral utilization of glucose (Bonner-Weir, 2000).

According to results of extensive research, phyto-compounds of Lemongrass essential oil target and interact with three anti-diabetic nuclear proteins: PPAR-γ (peroxisome proliferator-activated receptor, gamma), PTP-1B (protein tyrosine phosphatase 1B), and DPP-IV (dipeptidyl peptidase IV, human incretin degrading enzyme). In humans, each of these proteins is encoded by a different gene which regulates gene expression of insulin secretion and glucose metabolism. The mechanism of PPAR-γ activation and DPP-IV inhibition may therefore regulate the hyperglycemia, lipogenesis and hypertriglyceridemia associated with type-2 diabetes (Combs, 2010). In a number of studies, citral, and especially geraniol and myrcene, demonstrated insulin secretagogue action and moderate hypolipidemic and hypoglycemic properties, which make the compounds of Lemongrass essential oil potential agents for general prevention and management of diabetes.

Summary

In spite of their variety and effectiveness, synthetic drugs used to deal with *Diabetes mellitus* may cause unwanted side effects including drug-induced hypoglycemia, fluid retention, liver malfunctioning, and weight gain. Use of essential oils as a potential tool to deal with this rising problem is a relatively safe and economical alternative. The anti-oxidant, hypoglycemic, hypolipidemic and anti-inflammatory properties of essential oils may be considered potential agents for the development of novel and side-effect free nutraceuticals and pharmaceutical preparations.

Géranium rosat © Laitche

Essential oils of Geranium rosat (*Pelargoium* species) (Rao et al, 2002), *Eucalyptus globulus* and *Cymbopogon citratus* used in Aromatherapy massage applications affect insulin sensitivity, glucose consumption and lipid accumulation activity, and can be potentially used for the prevention and management of different types of *Diabetes mellitus* and associated pathological conditions, as well as the development of novel types of effective and affordable phyto-pharmaceuticals.

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