A Systematic Review on Effect of *Scoparia Dulcis* on Alterations in Antioxidant Status, Oxidative Damage in Diabetes and Other Pharmacological Activities

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Abstract: Oxidative stress is implicated in the pathogenesis of diabetic complications. Diabetes mellitus is presently a burden not only on the individuals affected by the disease but also on society, particularly the national health system of all the countries. The war against diabetes through the development of new drugs is an ongoing continuous process. Despite many advances in the development of oral hypoglycemic agents, an ideal drug for treating diabetes mellitus is still a distant reality. As pointed out by World Health Organisation (WHO), prevention of diabetes and its complications is not only a major challenge for the future, but essential if health for all is to be attainable target. WHO study groups emphasize strongly in this regard the optimal, rational uses of traditional and natural indigenous medicine. The study of such medicinal plants might offer a natural key to unlock diabetologists pharmacy for the future. Indian traditional medicines have a long history to treat diabetic mellitus (DM) by the herbs and herbal extracts. *Scoparia dulcis*, also known as sweet broom weed, is a perennial herb which is commonly found in tropical and subtropical regions. In these regions, the fresh or dried plant has traditionally been used as one of remedies for diabetes and various diseases. The plant is abundantly found in many countries and can be easily grown and cultivated, should there be a need for mass production. The whole plant is used for ailments like diarrhea, stomach-ache, kidney stones, kidney problems, and fever. S. dulcis is a rich source of flavones, terpenes and steroids *S. dulcis* is one of the traditional antidiabetic herbs. There were so many research work done on its antidiabetic properties. *S. dulcis* has been used by human for centuries as a medicinal herb. *S. dulcis* has also been shown to exhibit analgesic, antimalarial, hepatoprotective, sedative, hypnotic, antiulcer, antisickling, and antimicrobial activities. Given this evidence, it may be concluded that *S. dulcis* could be promoted among the masses as an alternative and complementary therapy for diabetes, provided further scientific studies on the toxicological and pharmacological aspects are carried out through either *in vivo* or clinical means.

Introduction

Chronic hyperglycemia is the primer of a series of cascade reactions causing the over production of free radicals and increasing evidences indicate that these contributes to the development of diabetic complications (Baynes and Thrope, 1999). Defense system against oxidative attacks is usually able to buffer most ROS produced during physiological and pathological metabolism. However, the imbalance in scavenging of free radicals, due to an increase in oxidative flux or a decrease in the antioxidant ability is responsible for cellular and tissue damage in diabetes mellitus (Cakatay et al. 1995; Murugan, 2010).
Long established systems of traditional medicine have evolved from systematic recordings of human experience over several millennia (Hu et al. 2003). *S. dulcis* , a traditional Indian medicine herb, is considered as a useful medicine for the amelioration of diabetes (Nath 1943). It has been reported that *S. dulcis* has traditionally been used as one of remedies for stomach troubles (Satyanarayana 1969), hypertension (Chow et al. 1976), diabetes (Latha and Pari, 2004), inflammation (Gonzales Torres 1986), bronchitis (Farias Freie et al. 1993) hemorrhoids and hepatosis (Satyanarayana 1969) and as an analgesic and antipyretic (Gonzales Torres 1986). The active principles are scoparic acid A, scoparic acid B (Hayashi et al. 1993), scopadulcic acid A and B, scopadulciol (Hayashi et al. 1990) and scopadulin (Hayashi et al. 1991). These compounds were found to possess various biological activities for example as inhibitors against replication of herpes simplex virus, as gastric Hþ, Kþ ATPase activators and in antitumor promoting. Nath (1943) studied the antidiabetic effect of *S. dulcis* and obtained a glycoside, almelin, from fresh plant and reported that it brought relief in ailments accompanied with diabetes (ie., pyorrhoea, eye troubles, joint pain, susceptibility to cold etc.) within a very short period.

Streptozotocin (STZ) can result in the formation of ROS including H_2O_2, $O_2^{\bullet -}$, and $OH^{\bullet}$. STZ-induced oxidative damage includes the induction of macromolecular damage, depletion of cellular thiol levels and increase in lipid peroxidation with disturbance of antioxidant defense system including alteration in the activities of SOD, CAT, GPx and impaired GSH metabolism (Choudhary et al. 2002; Murugan, 2015a). Any compound natural or synthetic with antioxidant properties might contribute towards the partial or total alleviation of this damage may have a significant role in treatment of diabetes mellitus (Murugan, 2021b; Murugan, 2023a). The present section provides the antiperoxidative and antioxidant effect of *S. dulcis* in STZ diabetic rats.

Scoparia dulcis

S. dulcis is an annual erect herb distributed throughout tropical and subtropical regions of India, America, Brazil, West Indies, and Myanmar. The whole plant is used for ailments like diarrhea, stomach-ache, kidney stones, kidney problems, and fever. *S. dulcis* is a rich source of flavones, terpenes and steroids (Jain and Srivastava, 2006).

As a number of antihyperglycemic agents have been found in plants, research into understanding the scientific basis for plant-based traditional medicines from various cultures has increased. Scientists explore clues to discover new therapeutic drugs for type 2 DM (Murugan, 2015c). STZ is an antimicrobial agent and has also been used as a chemotherapeutic alkylating agent and reported as diabetogenic. Again, this insulinopenia syndrome, called 'STZ diabetes', is caused by the specific necrosis of the pancreatic beta cells and STZ has been the agent of choice for the induction of diabetes mellitus in animals ever since (Murugan, 2015d; Murugan, 2021c).

Indian traditional medicines have a long history to treat DM by the herbs and herbal extracts. *S. dulcis* is one of the traditional antidiabetic herbs. There were so many research work done on its antidiabetic properties (Murugan, 2021a; Murugan, 2015b). However, no one had studies its effect on enzymes α-amylase and α-glycosidase that regulate postprandial glucose absorption and metabolism and is responsible for postprandial hyperglycaemia. This study aimed to brief the antidiabetic properties of *S. dulcis* by correlating its antioxidant properties with *in vitro* and *in vivo* management of diabetes (Grover et al., 2002).

Sweet Broom Weed is a branched herb with wiry stems, growing up to 1 m tall. Small white, hairy flowers occur in leaf axils. The stamens are greenish and the ovary is green. Flower-stalk is 5-10 mm, hairless. Calyx is lobed to the base; sepals 4, ovate-oblong, about 2 mm, margin fringed with hairs, tip blunt. Flowers are white, about 4 mm across. Tube is densely hairy at throat, petals 2-3 mm, obovate roundish, upper petal slightly larger than others. Stamens protruding. Style erect. Narrowly elliptic, almost stalkless leaves are arranged oppositely or in whorls of 3. Leaves are 3-4 X 1-1.5 cm wide, with serrated margins. The capsule is nearly round. Sweet Broom Weed is native to Tropical & Subtropical America, widely naturalized in India and Africa.

S. dulcis fruits are brown capsules containing brown seeds. It is considered a weed in many areas but used as medicinal herb for a wide range of uses including treatment for digestive problems, pulmonary conditions, fever, skin disorders, hypertension, hemorrhoids, diarrhea, dysentery, insect bites, anemia, albuminuria, diabetes, herpes, etc. Seed infusion can be drunk. The leaves are used to sweeten well water and for tea and young shoots can be consumed as vegetable. The bushy stems are used as temporary brooms. Fresh or dried plants reportedly kill fleas, lice, and intestinal worms. Plant can be grown from seeds (Latha and Pari, 2003).

Medicinal uses: It is traditionally used in treatment of diabetes, dysentery, earache, fever, gonorrhea, headaches, jaundice, snake bite, stomach problems, toothache and warts.

Details

Family	Plantaginaceae
Species	*Scoparia dulcis* L.
Weed type	Broadleaf
Stem	The stem is polygonal and full. It is often woody at the base. It is hairless.
Leaf	The leaves are opposite or verticillate in three. They are simple and sessile. The lamina is oblanceolate, 2.5 to 5 cm long and 1.5 cm wide. The base is attenuated by acute corner, forming a pseudo-petiole. The top corner is wide. Both sides are smooth and riddled with green glands, brilliant. The margin is entire in the lower half of the leaf blade and toothed in the upper half.
Flower	They are a bluish color. They are carried by a peduncle 6 to 8 mm long. The calyx consists of 5 sepals almost free to the base. They are elliptical in shape, tapering at the top. They are finely hairy. The corolla consists of 4 petals, rarely 5, free nearly to the base. They are oval, apiculate at the top. The entire calyx and corolla is 3 to 4 mm long. The four stamens have anthers 2-celled equal. The ovary is surmounted by a filiform style not exceeding the corolla.
Fruit	The fruit is a dehiscent capsule, ovoid, surmounted by the style. It is 4 mm long and contains numerous seeds. When ripe, it opens in two valves.
Seed	The seeds are extremely small, they measure 0.1 mm long. They are obconical shape.
Biology	*S. dulcis* is an annual to perennial species depending on conditions of soil moisture. It multiplies primarily by seed.
Ecology	Fallow fields, roads, old walls, in ever wet regions or not too dry regions with a prolonged dry season; on all kinds of soils, from 0-1600 m alt. Upland and rice fields.
Origin	Originating in tropical America.
Use	Leaves are used in treatment of fever, cough, bronchitis and dental trouble. Leaves and stems are used for diabetes.

Chemical constituents

There are 115 compounds in *S. dulcis* that have therapeutic potential for the treatment of metabolic syndrome. The chemical structures of compounds in *S. dulcis* are listed in the following section. These chemical substances can be roughly divided into the following categories: nitrogen-containing compounds, flavonoids, diterpenoids, triterpenoids, steroids, phenolics, and other aliphatics. So far, the flavonoids, diterpenoids, and alkaloids contained in *S. dulcis* are the most diverse. Each of the compounds has been marked with a number (Freire et al., 1996), and some of them have defined unique biological activities. The antidiabetic, hypolipidemic, anti-inflammatory, and antioxidative effects of these compounds are the molecular basis for the use of *S. dulcis* in the treatment of metabolic syndrome. The compounds are extracted from different parts of *S. dulcis*, including the whole plant, aerial parts, leaves, and roots. Most of the compounds are isolated from the leaves of *S. dulcis*. The pharmacological activities of some compounds need to be further studied, and some compounds are expected to be further researched and developed as medicines for the treatment of metabolic syndrome.

It has a very wide range of uses in tropical America where it is used to treat conditions such as digestive problems, pulmonary complaints, fevers and skin disorders (Hayashi et al., 1988),. The plant is seen as an antibilious, antibiotic, antidote, aphrodisiac, bitter, blood purifier, emetic, febrifuge, hepatic, hypoglycaemic and stomachic (Mahato et al., 1981). The roots, leaves and tops are traditionally used in India, Indo-China and South-East Asia as an analgesic, diuretic and antipyretic, to treat gastric disorders such as diarrhoea and dysentery, and also for cough, bronchitis, hypertension, haemorrhoids and insect bites. Research has shown that the plant contains a number of medically active compounds - the aerial parts contain about 4% of a viscous oil which, besides fatty acids like stearic, myristic and linolenic acid, also contains a series of diterpenes (Pari and Venkateswaran, 2002). The aerial parts also yield nitrogen-containing components and flavonoids (Satyanarayana et al., 1969). Scopadulin, a diterpene from the aerial parts, has shown mild antiviral activity (Ahmed et al., 1990). The antiviral activity of scopadulciol, a tetracyclic diterpenoid, was found to inhibit the virus replication, as shown by reduction of virus production (Mahato et al., 1981).

Scopadulcic acid B has been shown to have a tumour-inhibiting action and has also been shown to inhibit replication of herpes simplex virus type 1(Pari and Venkateswaran, 2002). The fresh stems and leaves contain a compound called amellin, thought by some to have an important therapeutic action in diabetes; however, others doubt this. Oral administration of amellin relieves symptoms of glycosuria, reduces hyperglycaemia and increases RBC count. It has also been found helpful in anaemia, albuminuria, ketonuria, retinitis and other complications associated with diabetes mellitus. Unlike insulin, amellin does not cause blood sugar levels to drop below normal and reduction of both blood and urine sugar occurs gradually (Aysha Reem et al., 2020).

The whole plant is used for treating a wide range of disorders including diabetes, herpes, coughs and colds, fevers, nausea, dizziness, and as an antidote for snakebites and cassava intoxication. In low doses, often in milk, it is used to relieve vomiting in infants, whilst in larger does it is used to induce vomiting to clear out the digestive system (Latha and Pari, 2004). A decoction of the plant is drunk as a treatment for remittent fever and gonorrhoea, and also to induce labour. A cold decoction of the plant is taken as a remedy for gravel and kidney complaints (Latha and Pari, 2003).

The fresh or dried plants are used externally to treat a wide range of skin problems, including pimples, impetigo, ulcers, eczema, bruises and contusions. An infusion of the herb is used as a mouthwash for infected gums (Pari and Latha, 2003). The leaves are chewed to treat cough; they first taste bitter and later sweet (like liquorice). They were formerly used in the treatment of diabetes. The leaves are macerated in warm water and drunk copiously when cooled in the treatment of feverish headaches (Pari et al., 2004).

Thiobarbituric acid reactive substances (TBARS) and hydroperoxides

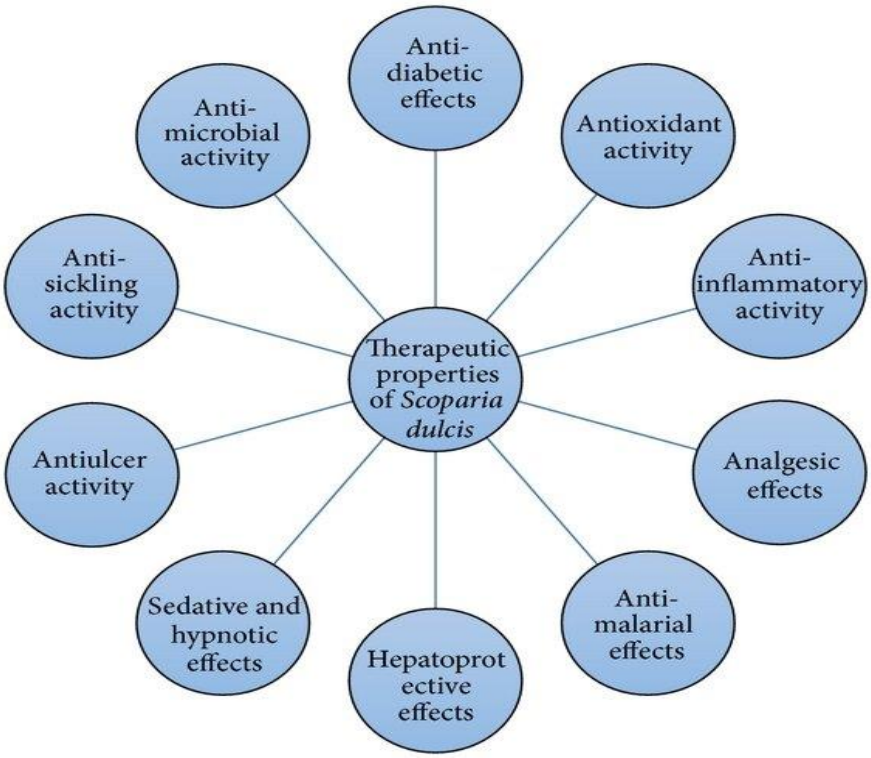
Lipid peroxidative markers namely: TBARS and hydroperoxides in plasma and tissues of diabetic control rats were significantly increased. Treatment with *Scoparia dulcis* extract (SPEt) and glibenclamide significantly reduced the levels of lipid peroxidation products (Latha and Pari, 2003).

Enzymic and non-enzymic antioxidants

For studying the effect of SPEt on free radical production and its effect on antioxidants, the activities of SOD, CAT, GPx, GST, GSH, vitamin C, vitamin E and ceruloplasmin were measured. The levels of enzymic and non-enzymic antioxidants were significantly decreased with significant increase in ceruloplasmin level in diabetic control rats. The antioxidants levels were significantly increased in diabetic rats treated with SPEt. The extent of increase was higher in rats treated with of *S. dulcis* than glibenclamide treated rats (Latha and Pari, 2003).

Discussion

The involvement of free radicals in diabetes and the role of these toxic species in lipid peroxidation and the antioxidant defense system have been studied. STZ at a given dose preferentially destroys the pancreatic insulin secreting β-cells, which leaves less active pancreatic cells and results in diabetes mellitus (Murugan and Sakthivel, 2021). STZ directly generates oxygen free radical induced lipid peroxidation (Murugan, 2023a,b). This study was therefore undertaken to assess the antiperoxidative and antioxidant properties of *S. dulcis* in STZ diabetic rats.



Increase in hydroxyl radical formation in diabetic rats may be elucidated by two biochemical mechanisms. One mechanism is increased production of activated oxygen species such as $O2^{\bullet -}$ or H2O2. $OH^{\bullet}$ radicals are generated from $O2^{\bullet -}$ or H2O2 by the iron catalyzed Haber-weiss reaction or Fenton reaction respectively. Another mechanism is decrease in the activity of enzymes (SOD, CAT, glutathione dependent enzymes) to scavenge the activated oxygen species (Chiou et al. 2003). STZ-induced redox impairment could result from (a) an increase in the production of intracellular free radicals, either endogenous or exogenous (eg. STZ itself) (b) second from a STZ-induced decrease in the ability of the cell to maintain antioxidant mechanisms (eg. inability to maintainreduced GSH concentration or a reduction in SOD activity) (Robbins et al. 1980). Hyperglycemia in the STZ treated rats leads to the formation of H_2O_2, which subsequently generates other free radicals. These reactive compounds can cause peroxidation of lipids resulting in the formation of hydroperoxy fatty acids and endoperoxides.

Lipid peroxidative markers

It has been generally reported that diabetic patients with vascular lesions have higher TBARS levels than their healthy counterpart. TBARS and hydroperoxides significantly increased in plasma of diabetic control rats. Previous studies have reported that there was an increased lipid peroxidation in plasma of diabetic rats (Murugan, 2022). Several studies have shown increased lipid peroxidation in clinical and experimental diabetes (Murugan, 2023 a,b). Lipid peroxide mediated tissue damages have been observed in the development of type 1 and type 2 diabetes mellitus (Feillet-Coudray et al. 1999).

Our results show increased lipid peroxidation in the tissues (liver, kidney and brain) of diabetic control rats. Previous studies have reported that there was an increased lipid peroxidation in liver, kidney and brain of diabetic rats (Murugan, 2015a; Pari and Murugan, 2007; Murugan and Pari, 2007; ;Murugan, 2023d). This may be because the tissues contain relatively high concentration of easily peroxidizable fatty acids. Liver during diabetes, showed a relatively severe impairment in antioxidant capacity than kidney. The kidney exhibits a characteristic pattern of changes during diabetes (Aragno et al. 1999). The Central Nervous System (CNS) is also susceptible to long term complications associated with diabetes (Aragno et al. 1997). Experimental models of diabetes including the STZ diabetic rats, have provided evidence for functional and morphological alterations in the brain (Biessels et al. 1994). Free radicals are formed in the CNS as part of the normal metabolic processes (Wolff, 1993). High oxygen uptake and low antioxidant defenses increase the vulnerability of the CNS to oxidative damage (McCall, 1992). The increase in oxygen free radicals in diabetes could be primarily due to increase in blood glucose levels, which upon autoxidation generate free radicals and secondarily due to the effects of diabetogenic agent STZ (Ivorra et al. 1989). Administration of SPEt and glibenclamide reduced the lipid peroxidative markers in plasma and tissues of diabetic rats.

Enzymic and non-enzymic antioxidants

Associated with the changes in lipid peroxidation, the diabetic tissues showed decreased activity of key antioxidants SOD, CAT, GSH, GPx, GST, GSH, vitamin C and vitamin E, which are playing important role in scavenging the toxic intermediates of incomplete oxidation. SOD and CAT are the two major scavenging enzymes that remove toxic free radicals in vivo. Previous studies have reported that the activity of SOD is low in diabetes mellitus (Vucic et al. 1997; Feillet-Coudray et al. 1999). Reduced activities of SOD and CAT in liver, kidney and brain have been observed during diabetes and this may result in a number of deleterious effects due to the accumulation of $O2^{\bullet-}$ and H_2O_2 (Searle and Wilson, 1981). Administration of SPEt significantly increased the activities of SOD and CAT. Therefore, removing $O2^{\bullet-}$ and $OH^{\bullet}$ is probably one of the most effective defenses against diseases (Lin et al. 1995). The result of increased activities of SOD and CAT suggest that SPEt contains a free radical scavenging activity, which could exert a beneficial effect against pathological alterations caused by the presence of $O2^{\bullet-}$ and $OH^{\bullet}$. The increased activity of SOD accelerates dismutaion of $O2^{\bullet-}$ to H_2O_2, which is removed by CAT (Aebi, 1984). This action could involve mechanisms related to scavenging activity of SPEt.

Under *in vivo* conditions, GSH acts as an antioxidant and its decrease was reported in diabetes mellitus (Baynes and Thrope, 1999). We have observed a significant decrease in GSH levels in liver, kidney and brain during diabetes. The decrease in GSH levels represents increased utilization due to oxidative stress (Murugan and Sakthivel, 2022). The pathophysiological consequence owing to depletion of GSH has been well studied. The depletion of GSH, GPx and GST in tissues promotes generation of ROS and oxidative stress with cascade of effects thereby affecting functional as well as structural integrity of cell and organelle membranes (Raza et al. 2000). It has been proposed that GPx is responsible for the detoxification of H_2O_2 in low concentration whereas CAT comes into play when GPx pathway is reaching saturation with the substrate (Salahudeen, 1995). Furthermore, the decreased lipid peroxidation is correlated well in accordance with the induction of antioxidant enzymes above basal level. Murugan (2015a) reported that GPx has broader protective spectrum than CAT in catalyzing the reduction of both H_2O_2 and other hydroperoxides. Treatment with SPEt increased the GSH, GPx and GST activities. The elevated level of GSH protects cellular proteins against oxidation through glutathione redox cycle and also directly detoxifies ROS generation from exposure to STZ (Yu, 1994).

Ascorbic acid is a potent antioxidant, which widely acts on OFR as well as interact with vitamin E (Garg and Bansal, 2000). Vitamin E levels in platelets are reduced in diabetes. Both the vitamins-C and E significantly decreased in plasma of diabetic control rats. Low levels of plasma antioxidants have been implicated as a risk factor for the development of diabetes (Vatassery et al. 1983). It has been suggested that vitamin E deficiency may be one of the factors in the pathogeneseis of abnormalities of diabetic microvascular flow (Watanabe et al. 1984). Previous studies demonstrate the reduced plasma concentration of vitamin C in diabetes (Jennings et al. 1987; Lindsay et al. 1998). Oxidative stress, increased polyol pathway, non-enzymic glycation of proteins and disturbed vitamin C metabolism may be important in the pathogenesis of diabetic microangiopathies (McLennan et al. 1991). Administration of SPEt increased the vitamin C and E levels. This indicates that vitamin E is used in combating free radicals and if vitamin C is present, vitamin E levels are preserved. Frei (1991) has previously shown the ability of vitamin C to preserve the levels of other antioxidants in human plasma. Also vitamin C regenerates vitamin E from its oxidized form. GSH is the first line of defense against pro-oxidant status (Ahmed et al. 2000) and GSH was elevated after SPEt administration. GSH systems may have the ability to manage oxidative stress with adaptional changes in enzymes regulating GSH metabolism. In the present study, treatment with SPEt significantly increased the GSH levels. Increase in GSH level may inturn activates the GSH dependent enzymes such as GPx and GST.

Reduced levels of vitamin C and vitamin E in liver, kidney and brain were observed during diabetes in our study. Both vitamin C and E are known to prevent detectable lipid peroxidation and under physiological conditions, it has been suggested that vitamin C helps to recycle vitamin E from its radical form (Garg and Bansal, 2000). Higuchi observed a decrease in hepatic vitamin E levels in rats with STZ diabetes (Higuchi, 1982). Reduced levels of vitamin C and E in tissues were reported by Murugan and Sakthivel, (2021) in diabetic rats. Treatment with SPEt increased the vitamin C and E levels.

Ceruloplasmin is an important enzyme, which oxidizes iron from the ferrous to ferric state and it has been demonstrated that iron catalyzed lipid peroxidation requires both Fe (II) and Fe (III) and the maximum rate occurs when the ratio is approximately one (Bucher et al. 1983). The level of ceruloplasmin is reported to increase under diseased conditions leading to the scavenging of oxygen products such as $O2^{\bullet-}$ and H_2O_2 (Dormandy 1980). The observed increase in the level of plasma ceruloplasmin in diabetic rats may be due to increased lipid peroxides. Oral administration of SPEt to diabetic rats restored the level of ceruloplasmin to near normal level.

Administration of SPEt increased the activity of antioxidants and may help to control free radical, as *S. dulcis* has been reported to be rich in diterpenoids and flavonoids, well-known antioxidants (Hayashi et al., 1990, 1991, 1993), which scavenge the free radicals generated during diabetes. Since the study of induction of the antioxidant enzymes is considered to be a reliable marker for evaluating the antiperoxidative efficacy of the medicinal plant, these findings are suggestions of possible antiperoxidative role played by *S. dulcis* plant

extract. It is possible therefore, that the increased levels of free radical scavenging enzymes may act as an added compensation mechanism to maintain the cell integrity and protection against free radical damage.

Hepatoprotective effect of *S. dulcis*

Metabolic diseases are prone to the non-alcoholic fatty liver disease (NAFLD). *S. dulcis* has been used to treat this disease (Wan et al., 2015). Therefore, some research achievements verified this herbal hepatoprotective activity by using various extracted ingredients of the herb, such as whole plants, roots and foliar, using a variety of organic solvents.

Toxicological studies

The toxicity of coixol was evaluated in the *in vitro* MTT assay and showed nontoxic in both MIN-6 and 3T3 cell lines (IC_{50} > 200 μM). Acute and subacute toxicity evaluated in mice showed no significant changes in serum creatine, ALT, and AST, no other abnormal manifestation and no death at 100 mg kg^{-1} body weight, suggesting that coixol was nontoxic in kidney and liver (Sharma Khaga et al., 2015). Coixol administered intravenously showed no toxic effects (Senadheera et al., 2015). Mice treated with 20, 100, and 500 mg kg^{-1} of coixol also exhibited no toxic manifestations. Ethanolic extract of whole plants of *S. dulcis* (EESD) exhibited no toxic effect after the observation period of 72 h when administered orally at doses of 1000, 2000, and 3000 mg kg^{-1} (Moniruzzaman et al., 2015). The aqueous extract of *S. dulcis* at a dosage of 8 g kg^{-1} administered orally exhibited no mortality, no changes in posture, motor activity, and behavior in rats compared to the control group. The 30 days' administration of the extract did not show any gross poisoning symptoms or deaths, but histopathological examination showed mild portal, vascular, stroma, and interstitial congestion in liver, heart, testis, and lung respectively (Abere et al., 2015).

Analgesic and anti-inflammatory activity

The diterpene scoparinol demonstrated significant analgesic ($p<0.001$) and anti-inflammatory activity ($p<0.01$) in animals. Pretreatment of ethanolic extracts of S. dulcis (0.5 g kg-1) reduced acetic acid-induced writhing in mice 47%. The extract (0.5 and 1 g kg-1) also inhibited paw edema in rats induced by carrageenan 46 and 58%, respectively after 2 h. The triterpene glutinol (30 mg kg-1) reduced writhing in mice induced by acetic acid 40% and paw edema in rats induced by carrageenan 73%, indicating that the analgesic activity of S. dulcis is most likely related to the anti-inflammatory activity of glutinol (Freire et al., 1991).

Antiviral activity

In vitro the diterpenoid scopadulcic acid B inhibited viral replication of herpes simplex virus type 1 in a hamster test model. The mechanism of action is unknown but does not involve a direct virucidal effect or inhibition of virus attachment. Topical application or intraperitoneal injections at 100 and 200 mg/kg/day prolonged the development of herpetic lesions and survival time when treatment was initiated immediately after virus inoculation (Hayashi et al., 1988).

Anti-malarial activity

In vitro the diterpenoid scopadulcic acid A has activity against various Plasmodium falciparum isolates with an IC_{50} of 27 mcM against the D6 clone (African Sierra isolate) and an IC_{50} of 19 mcM against the W2 clone (Indochina isolate). The IC_{50} against the multidrug-resistant TM91C235 (Thailand) isolate was 23 mcM. For comparison, IC_{50} values for chloroquine were 9.3, 266 and 24 nM against D6, W2 and TM91C235. The IC50 values for mefloquine were 36, 4.8 and 59 nM against D6, W2 and TM91 C235 (Riel et al., 2002).

Neurotropic activity

***In vitro* data:** The acetylated flavone glycosides from *S. dulcis* have NGF-potentiating activity, which may be useful in treating neurological disorders. In control experiments, following incubation, the percentages of neurite-bearing cells in PC12D cells were 27% with 2 ng mL^{-1} NGF and 71% with 30 ng mL^{-1} NGF after 48 h. After incubation with the glycosides from S. dulcis, neurite outgrowth in PC12D cells was increased by an additional 16 and 15%, respectively (Li and Ohizumi, 2004; Li et al., 2004).

Anti-cancer activity

In vitro and in vivo: Scopadulcic acid B inhibited the effects of the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA). Scopadulcic acid B also inhibited TPA-enhanced phospholipid

synthesis in cultured cells and inhibited the effect of TPA on skin tumor formation in mice initiated with 7, 12 dimethylbenz (a) anthracene (Nishino et al., 1993). Four new labdane-derived diterpenes, isolated from the aerial parts of S. dulcis, were cytotoxic against the following 6 human stomach cancer cell lines: SCL, SCL-6, SCL-37'6, SCL-9, Kato-3 and NUGC-4. Vinblastine sulfate and mitomycin C were used as positive controls. Scopadulcic acid C, another diterpene, enhanced the antitumor efficacy of acyclovir and ganciclovir in a HSV-TK gene therapy system. The synergistic activity was caused by the activation of viral thymidine kinase (Nkembo et al., 2005).

Other pharmacological activity

In an animal study, an aqueous fraction of *S. dulcis* revealed the presence of 2 catecholamines, noradrenaline and adrenaline, that may account for the hypertensive and inotropic effects after parenteral administration (De Farias Freire et al., 1996). A significant effect on onset and duration of sleep ($p<0.05$) was caused by scoparinol on pentobarbital-induced sedation in animals. In another animal study, sleeping time induced by sodium pentobarbital 50 mg kg-1 was prolonged 2-fold in mice pretreated with 0.5 g kg-1 of an ethanolic extract of S. dulcis. Scoparinol has a diuretic action in animals as demonstrated by the measurement of urine volume after administration (Ahmed et al., 2001; Freire et al., 1991). The flavones glycosides, including isovitexin, inhibit activity against β-glucuronidase (Kawasaki et al., 1988).

Conclusion

This review discusses the antidiabetic activities of *S. dulcis* as well as its antioxidant and anti-inflammatory properties in relation to the diabetes and its complications. *S. dulcis* possess beneficial activities like normalizing carbohydrate and lipid metabolism, improving the number of receptor sites per cell and affinity of the erythrocyte by its insulin secretagogue effect has hampered *S. dulcis* as an antidiabetic drug. Ethno medical applications of the herb have been identified as treatment for jaundice, stomach problems, skin disease, fever, and kidney stones, reproductory issues, and piles. Medicinal herb for a wide range of uses including treatment for digestive problems, pulmonary conditions, fever, skin disorders, hypertension, hemorrhoids, diarrhea, dysentery, insect bites, anemia, albuminuria, diabetes, herpes, etc. Thus, findings and explanation regarding *S. dulcis* suggest that it may safely be implicated as an antioxidant agent in addition to its antidiabetic effect that may be used for therapeutic purposes.

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