Alternate therapy of Type 2 diabetes mellitus (T2DM) with Nigella (Ranunculaceae)

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Type 2 diabetes mellitus (T2DM) is being more incurable due to its complex patho-physiology and failure of conventional anti-diabetic agents to restore the normal architecture and morphology of pancreatic islets and some potential side effects and weight gain. Many agents of plant origin have been used as anti-diabetic agents since ancient time. Among them Nigella sativa L. (Ranunculaceae) is being more popular day by day due to its potential and broad spectrum effects on many diseases but unfortunately, no sufficient scientific data is available. A comprehensive literature (in English only) search was conducted using electronic databases: Medline (1966 to 2010) and EMBASE (1980 to 2010). For a simple search, initially the search terms used were “anti-diabetic agent,” and “N. sativa,” for each search term separately, and then an advanced search was made by combining all search fields in abstract, key words, or title. Recently, a lot of work has been done for the evaluation of anti-diabetic (against type-II diabetes) effect of N. sativa, significant results have been achieved. However, further studies are required to investigate the anti-diabetic (against type-II diabetes) of N. sativa at molecular levels.

Key words: Anti-diabetic agent, in vitro analysis, in vivo studies.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by the hyperglycemia, dyslipidemia and imbalanced pro-inflammatory/oxidative mediators along with various transcriptional pathways that decisively provoke the impairment of pancreatic islets and their apoptosis, and ultimately overt diabetes, and affects millions of people every year. The prevalence of diabetes is increasing worldwide (Wild et al., 2004) and among the cases of diabetes make a diagnosis, more than 95% are T2D (Sachdeva et al., 2009), and it is unspecified that if its pervasiveness is not stopped properly then it may have an effect on more than 366 million population in 2030 (Wild et al., 2004). It is one of the 5 major causes of the death in the world (Rahimi et al., 2005). Among various factors that are being involved in the progression of T2DM, oxidative stress plays its crucial role in the etiology of diabetes and diabetic complications (Noor et al., 2008; Prasad et al., 2009) and it not only damage function of islets but also demolish them (Martim et al., 2003). From various studies performed on alloxan or streptozotocin (STZ) induced diabetic rats and mice
(Bhatti et al., 2009) and some diabetic patients, high insensitivity of oxidative stress due to persistent and chronic hyperglycemia, deplete the activity of anti-oxidative defense mechanism by promoting the generation of free radicals (Baynes, 1991). STZ induced diabetic animals have also been used to investigate the effect of diabetes on the induction of neuropathy (Jakobsen and Lundbaek, 1976; Sharma et al., 1977), and certain interactive pathogenic mechanisms of diabetic peripheral nephropathy have been developed both in human and experimental animal models, and chronic hyperglycemia have been considered as primary risk factor for the induction of nephropathy. This chronic hyperglycemia could augment the enhanced oxidative stress, increased aldose reductase activity (Cameron et al., 1997), and cause the accumulation of advance glycation end products (Karachalias et al., 2003).

Majority of infections are at the epidemic levels in the world, although a variety of drugs have been discovered from natural source or are being synthesized in the laboratories for the treatment of these chronic diseases but their side or adverse effects are overall off-putting the clinical uses of these medicines. For its traditional therapy, many agents of plant origin along with synthetic agents are also being used for the treatment of T2DM (Arayne et al., 2007). According to the world ethnobotanical report, almost 800 plants posses antidiabetic potential (Alarcon-Aguilera et al., 1998) and due to known potential, known complications such as known toxicity (Kahn et al., 2006; Alvarsson et al., 2008; Yki-Järvinen, 2004), and weight gain during therapy (DeFronzo et al., 2011; McFarlane, 2009; Purnell and Weyer, 2003; Bonora, 2007; Mitri and Hamdy, 2009) with conventional anti-diabetic agents, research has been focused on scientific evaluation of traditional drugs of plant origin and trying to screen out more effective and safe hypoglycemic agents (Arayne et al., 2007), and open new door for the investigators and researchers to think about these traditional anti-diabetic plants with histories thousands years back due to their traditional uses when synthetic agents have not been invented. Yet in developing countries, almost 80% population still use these plants in primary medical problems (Grover and Yadav, 2004; Paarakh, 2010) and such remedies remain important in many developing and developed countries despite the lack of scientific study. Since 1980, World Health Organization (WHO) has started to encourage countries to investigate these traditional medical plants, however, evaluation of their active constituents has also open immense area for research and development (Paarakh, 2010).

MATERIALS AND METHODS

A comprehensive literature (in English only) search was conducted using electronic databases: Medline (1966 to 2010) and EMBASE (1980 to 2010). For a simple search, initially the search terms used were “anti-diabetic agent,” and “Nigella sativa,” for each search term separately, and then an advanced search was made by combining all search fields in abstract, key words, or title. To make certain a comprehensive review, investigation of literature was supplemented by probing the reference lists of the papers created from the original investigations. The authors selected the potentially appropriate papers identified by the electronic searches. The published literature eligible for inclusion were reviewed, in vitro and in vivo studies and the randomized trials are presented in English language. All the literature selected was confirmed for duplications, which, if observed were excluded.

RESULTS

Nigella sativa

N. sativa L. (Ranunculaceae) is a herbal plant known as black cumin (Arayne et al., 2007), most commonly cultivated in Europe, Middle East and Asia, and is most commonly used as traditional medicine in Arabian countries, the subcontinent and Europe (Sayed, 1980). In subcontinent, it is known as Kalonji or kalajeera while in China it is referred as Hak Jung Chou (Mathur et al., 2011). Recently, its pharmacological and potential therapeutic activities have also been proved for the treatment of many diseases such as bronchodilatation, immunomodulative (El-Kadi and Kandil, 1987), antibacterial (Hanafy and Hatem, 1991), hypotensive (Zaoui et al., 2000), hepatoprotective (Kanter et al., 2003, 2005a), gastroprotective (Kanter et al., 2005b), antihistaminic and anti-oxidative (Kanter et al., 2006a) and neuroprotective (Kanter et al., 2006b). According to Islam, it can cure all diseases except death (Paarakh, 2010). Even though, this plant has many beneficial effects to avert many chronic diseases but unfortunately, these effects have not been satisfactorily scrutinized. Only limited studies are available for the use of N. sativa as anti-diabetic agent in some diabetic patients to maintain the normoglycemia (Tahraoui et al., 2007; Otoom et al., 2006), and also there is no sufficient data available about the effect of N. sativa on the diabetic induced complications and syndromes.

Anti-diabetic properties of Nigella sativa

N. sativa is being used as antidiabetic agent since ancient time but unfortunately, no one has ever focus on this plant to study how and under which mechanism, could cause the normoglycemia. Recently, in this decade, numerous studies have been performed on experimentally induced diabetic animals (Mathur et al., 2011) to check its effects on diabetes and confirmed that this plant has also anti-diabetic activity as it reduced the significant levels of blood glucose in these animals (Fararh et al., 2002, Rchid et al., 2004, Kaleem et al., 2006; Kanter et al., 2003). These anti-diabetic properties of N. sativa plant are due to insulinotropic action (Fararh et al., 2002; Rchid et al., 2004), anti-oxidant properties
Several studies have also been performed to confirm its effects on insulin sensitivity and release (Farrah et al., 2002; Kanter et al., 2004; Benhaddou-Andaloussi et al., 2008, 2010). Recently, some studies have also been conducted on N. sativa and, they proposed that this plant improves insulin sensitivity by preventing the intensity of oxidative stress (Bloch-Damti and Bashan, 2005; Houstis et al., 2006; Song et al., 2007). From the results of the studies, it has been observed that N. sativa improves insulin sensitivity in peripheral tissues and enhances its secretion in the β-cells of pancreatic islets (Kanter, 2008; Bamosa et al., 2010; Sankaranarayanan and Pari, 2011), because it has been proposed that N. sativa has the ability to restore the structural integrity of the pancreatic islets in diabetic rats (El-Zawahrawy and Al-Zahra, 1998) and STZ induced diabetic rats (Kanter, 2008), and later some histopathological and immunohistochemical studies have been performed in order to investigate the architecture of pancreatic islets and observed that N. sativa has the ability to recover the integrity of β-cells of pancreatic islets (Benhaddou-Andaloussi et al., 2008, 2010; Kanter et al., 2009).

Insulin secretory effects of N. sativa have also been checked on in vitro isolated rat pancreatic islets in the presence of 8.3 mmol/L glucose and observed that secretion of insulin is increased in the presence of N. sativa (Rchid et al., 2004, Benhaddou-Andaloussi et al., 2008, 2010). It has been proposed from previous studies that reactive oxygen species (ROS) are generated by chronic exposure of hyperglycemia and that ROS are directly neurotoxic and promotes neuronal apoptosis (Luo et al., 1998; Kanter, 2008). N. sativa also has the ability to abate the diabetes associated complications, like diabetic nephropathy (Kanter, 2008). Results of these studies show that N. sativa has antidiabetic properties by different mechanisms (Benhaddou-Andaloussi et al., 2010).

In vitro and in vivo studies on Nigella sativa

Various in vitro and in vivo studies have also been conducted in order to confirm its antidiabetic effects on T2DM and diabetes associated complications but unfortunately on body the novel techniques used in order to find out its effects at molecular levels in different diseases. Conventional studies have been performed to confirm its traditional claimed effects. As we now know that T2DM is becoming more fatal disease, conventional therapies have failed due to some side effects (Kahn et al., 2006; Alvarsson et al., 2008; Yki-Järvinen, 2004; Li et al., 2003) and weight gain problems with some antidiabetic agents (DeFronzo et al., 2011, McFarlane 2009, Purnell, 2003; Bonora, 2007; Mitri and Hamdy, 2009), from now, we need such therapeutic agent which not only abate the infuriating effects of inducers of T2DM but also do not cause the weight gain during therapy. Various experimental studies have also been performed on N. sativa in order to point out any kind of cytotoxicity.

However, some possible cytotoxicity had been noted (Khader et al., 2007; IIaiyaraja and Khanum, 2010) which does not induce weight gain during therapy (Kanter 2008), thus, this drug will act as palliative for large number of chronic diseases and syndromes. Latest techniques are required to investigate the traditional effects of N. sativa on T2DM, diabetes induced complications and syndromes such as diabetic induced neuropathy and nephropathy. There is also need to investigate either N. sativa acts as therapeutic agent or its active constituent thymoquinone, induces its therapeutic activity.

Cross sectional survey and clinical trial of Nigella sativa

In south-eastern Morocco, N. sativa has been traditionally used for the treatment of diabetes and hypertension (Tahraoui et al., 2007), and in one cross sectional survey of 310 diabetic patients in Jorden, 7.3% were revealed to use N. sativa to treat diabetes (Ottoom et al., 2006). Recently, a double blind placebo controlled experimental trial was conducted in Indonesia and it was observed that N. sativa has the ability to significantly decrease the body weight but due to low dose, fasting of blood glucose along with lipid profile was not significant (Datau et al., 2010), and it has also been used in clinical trials for diseases other than diabetes (Mathur et al., 2011). Since this plant has no toxicity of kind (Ottoom et al., 2006; Bloch-Damti and Bashan, 2005), it does not induce the weight gain during therapy (Kanter, 2008) and it is being used as therapeutic agent for many diseases, and from the last decade, various studies are also being conducted to confirm its traditional effects on different diseases.

T2DM is manifestation of an autoinflammatory syndrome (Dinarello, 2011; Donath et al., 2008) which is usually associated with the state of low-grade inflammation in intra-islets (Holberg and Hotamisligil, 2006; Wellen and Hotamisligil, 2005). This low-grade inflammation is characterized by various factors such as IL-1β, TNF-α, IL-1 dependent cytokines and chemokines, elevated NF-κB activity, leptin, immune cells infiltration, amyloid deposits and fibrosis (Donath et al., 2008, Holberg and Hotamisligil, 2006; Wellen and Hotamisligil, 2005) and induces the β-cells dysfunction and apoptosis of these β-cells (Donath and Halban, 2004). So it is better.
way to use those agents that have the ability to abate this inflammation. It has been proved that N. sativa has anti-inflammatory properties (Al-Ghambi, 2001; Ali and Blunden, 2003; Tekoeoglu et al., 2007) but this anti-inflammatory property of N. sativa to reduce the intra-islet inflammation still needs to be confirmed, but it has been confirmed that thymoquinone the active constituent of N. sativa has the ability to reduce TNF-α and IL-1β in rheumatoid arthritis (Salem, 2005; Tekoeoglu et al., 2007) N. sativa has antioxidant properties and due to this effect, it improves glycemia (Kanter, 2008) but further studies are also needed to investigate if N. sativa has ability to reduce pro-inflammatory cytokines which are the main inducers of T2DM or not and if it has, then, which mechanism is involved to reduce these pro-inflammatory cytokines. So, we suggest that molecular level studies are needed to confirm its broad spectrum effects not only on T2DM but on various diseases in which N. sativa is traditionally used as palliative to cure these diseases.

Conclusion

Anti-diabetic effects of N. sativa has been studied in the recent years and satisfactory results have obtained but still, it is unclear under what exactly mechanism, it averts the symptoms of diabetes. Furthermore, pre-clinical and clinical trials are needed to confirm its exact mechanism against T2DM.

REFERENCES


