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Review: Shilajit (Mumie) A natural Product with Anti-hyperglycemic, Anti-obesity, Anti-oxidant, and Anti-Inflammatory properties for a potential treatment of diabetes mellitus

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Abstract

Diabetes is a major health problem worldwide that hinders normal life. Diabetes is a leading cause of death with high prevalence across the globe. Many drugs are used for the management of type 2 diabetes, unfortunately with some side effects including abdominal pain, kidney, liver, heart complications, and most commonly life-threatening hypoglycemia. Furthermore, these medications mitigate hyperglycemia symptoms and do not address the root cause, which is lipid accumulation in the pancreas, liver, and muscles. Therefore, there is a need for a safe natural product that manages diabetes and reduces obesity with fewer side effects. Shilajit, which is an exudate from many rock layers of mountains, especially the Himalayas, is made up of plant and microbial metabolites, including a mixture of organic humus, humic acid, fulvic acid, and minerals. It was used for many ailments in old traditional medicine and in current human and animal studies, in which its safety and fewer side effects were affirmed. Shilajit has anti-diabetic properties that include anti-hyperglycemia, anti-obesity, anti-oxidant, anti-inflammatory effects, increased metabolism, and important minerals. Anti-hyperglycemia of shilajit could be due to decreasing oxidative stress, decreasing inflammation, and increasing metabolism that leads to the burning of fat and decreasing obesity; all of these are implicated in insulin resistance and diabetes. Other uses of Shilajit include treatment of cancer, allergy, and increased immunity. More clinical studies are required to explore the mechanisms and benefits of Shilajit, as recent research is promising.

Keywords: Shilajit (Mumie); Diabetes mellitus; Anti-hyperglycemia; Anti-inflammatory; Anti-oxidant; Anti-obesity; Insulin sensitivity.

1. Introduction

Diabetes is an alarming health problem worldwide; it caused 1.5 million deaths in 2019 alone, with a prevalence of 8.5% for ages 18 and older and 422 million cases in 2014 (World Health Organization, 2019). Diabetes is a chronic, endocrinological, metabolic disorder (Trivedi et al., 2004) characterized mainly by hyperglycemia. Other symptoms include frequent urination, thirst, hunger, fatigue, blurred vision, and restlessness (Ramachandran, 2014; World Health Organization, 2019). Elevation of blood glucose levels in diabetes mellitus is due to insufficient pancreatic insulin secretion or insulin resistance by target cells (Piero et al., 2015). There are many types of diabetes: type 1 diabetes, type 2 diabetes, and gestational diabetes (Piero et al., 2015). Type 1 diabetes is an autoimmune disease against beta-pancreatic cells, and therefore is associated with insulin deficiency (DiMeglio et al., 2018). Type 2 diabetes is characterized by insulin resistance and beta cell dysfunction in the pancreas (Hameed et al., 2015). Most diabetes cases (around 90%) are of type 2 diabetes, and it was estimated in 2018 with 500 million cases worldwide (Kaiser et al., 2018; World Health Organization, 2016). According to the International Diabetes Federation (IDF), it is estimated that there will be 582 million adults living with diabetes worldwide in 2022. Of these, approximately 90% will have type 2 diabetes (Atlas, 2019).

There are many risk factors associated with diabetes, such as age, genetic factor or family history, lifestyle, physical inactivity, smoking, as well as obesity, and being overweight, which increase the risk of diabetes mellitus (World Health Organization, 2016). Furthermore, inflammation (Halim & Halim, 2019; Oguntibeju, 2019) and oxidative stress (Asmat et al., 2016; CHANDRA et al., 2019) are risk factors for the development of diabetes mellitus.

Chronic diabetes can lead to dangerous and life-threatening complications including hypertension, coronary heart disease, stroke, neuropathy, renal failure, cancer, retinopathy, obesity, proteinuria, hypertriglyceridemia, amputations, and foot ulcers (Basit et al., 2004; Harding et al., 2019; Stolar, 2010). The 5-year total cause mortality rate for diabetes type 1 and type 2 was estimated at 5.5 and 18.9%, respectively (Cusick et al., 2005). The diagnosis of diabetes includes a fasting plasma glucose test, random plasma glucose test, oral

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glucose tolerance test, and HbA1C test (Cox & Edelman, 2009).

Diabetes mellitus must be managed to prevent the progression of complications, mainly in type 1 diabetes mellitus, by using insulin replacement therapy, while diet, lifestyle changes, increased exercise, weight loss, and oral medication are considered for the treatment and management of type 2 diabetes mellitus (Bastaki, 2005). Insulin is also important in type 2 diabetes mellitus when blood glucose levels cannot be controlled; herbal supplements can also be useful in the management and treatment of diabetes (Bastaki, 2005). Medications used for diabetes include metformin, sulfonylurea, Glinides, thiazolidinediones, GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT2 inhibitors (Hu & Jia, 2019). Unfortunately, these medications have some side effects, and some of them have dangerous consequences, such as hypoglycemia, which could be fatal. Therefore, there is an urgent need for natural products to be safe and have no dangerous side effects.

2. Diabetes medications side effects

Insulin is used as the first choice of treatment in type 1 diabetes and in some cases for type 2 diabetes, it has some side effects such as hypoglycemia, hyperinsulinemia, weight gain, and ketoacidosis (Chantelau et al., 1989; Wong et al., 2016). Metformin, which is used as a first-line drug to treat type 2 diabetes (Holman, 2007), has some side effects, including lactic acidosis (DeFronzo et al., 2016), diarrhea (Takemori et al., 2020), abdominal cramps (Li et al., 2011), nausea (Zheng et al., 2015), vomiting (Duong et al., 2013), flatulence (Saluja et al., 2020), and abdominal pain (Bolen et al., 2007). Furthermore, metformin is associated with vitamin B12 deficiency (Kumthekar et al., 2012). Sulfonylurea is associated with hypoglycemia (Middleton et al., 2017), weight gain (Hemmingsen et al., 2014), and digestive disorders (Confederat et al., 2016). It is also associated with higher mortality rates and cardiovascular events (Azoulay & Suissa, 2017). Glinides have some side effects similar to sulfonylurea, including hypoglycemia (Wei et al., 2019), weight gain (Kroon & Zhou, 2021), and cardiovascular disease (Lv et al., 2020). The use of thiazolidinediones was related to some undesirable effects such as hypoglycemia (Rizos et al., 2009), edema (Idris et al., 2012), weight gain (Wilding, 2006) , increased bone fracture (Billington et al., 2015), liver failure (Farley-Hills et al., 2004; Floyd et al., 2009), and heart failure (Hernandez et al., 2011). The GLP-1 receptor agonist has some unwanted effects such as hypoglycemia (Iorga et al., 2020), nausea, vomiting (Hayes et al., 2021), and diarrhea (Gilbert & Pratley, 2020). DPP-4 inhibitors are also implicated with some negative effects, such as the increased risk of heart failure (Scirica et al., 2013), hypoglycemia (Salvo et al., 2016), pancreatitis (Zheng et al., 2018), headache and nausea (Salvo et al., 2016). SGLT2 inhibitors have also accompanied some unwanted side effects such as hypoglycemia (Horii et al., 2020), genital infections (Scheen, 2019), urinary tract infections (Donnan et al., 2019), and ketoacidosis (FDA, 2015). These side effects of diabetes medications are summarized in table 1. Therefore, there is a need for safe and natural medication with fewer side effects to manage diabetes such as herbs.

Table 1. Some commonly used diabetes drugs and their possible side effects.

Diabetes drug	Side effects	References
Insulin	Hypoglycemia, hyperinsulinemia, weight gain, ketoacidosis.	(Chantelau et al., 1989; Wong et al., 2016)
Metformin	Lactic acidosis, diarrhea, abdominal cramps, nausea, vomiting, flatulence, vitamin B12 deficiency.	(Holman, 2007) (Takemori et al., 2020) (Li et al., 2011) (Zheng et al., 2015) (Duong et al., 2013) (Saluja et al., 2020) (DeFronzo et al., 2016) (Kumthekar et al., 2012)
Sulfonylurea	Hypoglycemia, cardiovascular events, weight gain, digestive disorders.	(Middleton et al., 2017) (Hemmingsen et al., 2014) (Confederat et al., 2016) (Azoulay & Suissa, 2017)
Glinides	Hypoglycemia, cardiovascular disease, weight gain.	(Wei et al., 2019) (Kroon & Zhou, 2021) (Lv et al., 2020)
Thiazolidinediones	Hypoglycemia, heart failure, edema, weight gain, increased bone fracture, liver failure.	(Rizos et al., 2009) (Idris et al., 2012) (Wilding, 2006) (Billington et al., 2015) (Farley-Hills et al., 2004; Floyd et al., 2009) (Hernandez et al., 2011)
GLP-1 receptor agonist	Hypoglycemia, nausea, vomiting, diarrhea.	(Iorga et al., 2020) (Hayes et al., 2021) (Gilbert & Pratley, 2020)
DPP-4 inhibitors	Hypoglycemia, increased risk of heart failure, pancreatitis, headache, nausea.	(Scirica et al., 2013) (Salvo et al., 2016) (Zheng et al., 2018)
SGLT2 inhibitors	Hypoglycemia, genital infections, urinary tract infections, ketoacidosis.	(Horii et al., 2020) (Scheen, 2019) (Donnan et al., 2019) (FDA, 2015)

Please note that these studies were done on human and animals in different situations

There has been increasing interest in herbal remedies among researchers in recent years in both human and animal studies, due in part to concerns about the safety and efficacy of synthetic drugs (Al-Shudiefat et al., 2022; Newman & Cragg, 2020; Payab et al., 2020). Herbs can be used as anti-hyperglycemic and anti-hypertensive agents, due to biological actions and chemical composition (Eff et al., 2020). Shilajit is one of the herbomineral supplements that could be used for the treatment of diabetes in both humans and animals (Kanikkannan et al., 1995; Saxena et al., 2003).

3. Shilajit's physical properties and safety

Shilajit has many names (mumie; *Asphaltum Punjabianum* (scientific name), shilajatu, mumijo, mumiyo, mineral pitch, momiai, tasmayi, salajit, Hajar-ul-musa, Arakul dshibal, and mimie) (Ghosal et al., 1991; Khakimov, 1974; Kizaibek, 2013; Mishra et al., 2019; Stohs, 2014). The use of these different names of Shilajit in Google Scholar, PubMed database, and commercially on Ebay are shown in Figures (1 + 2), with Shilajit being the most common name used in all. Three famous online websites were initially assigned to search for shilajit products, these are (Amazon, Alibaba, and Ebay). After searching for shilajit products on these online websites, Ebay online website was chosen, because the number of shilajit products was much higher on Ebay than the others.

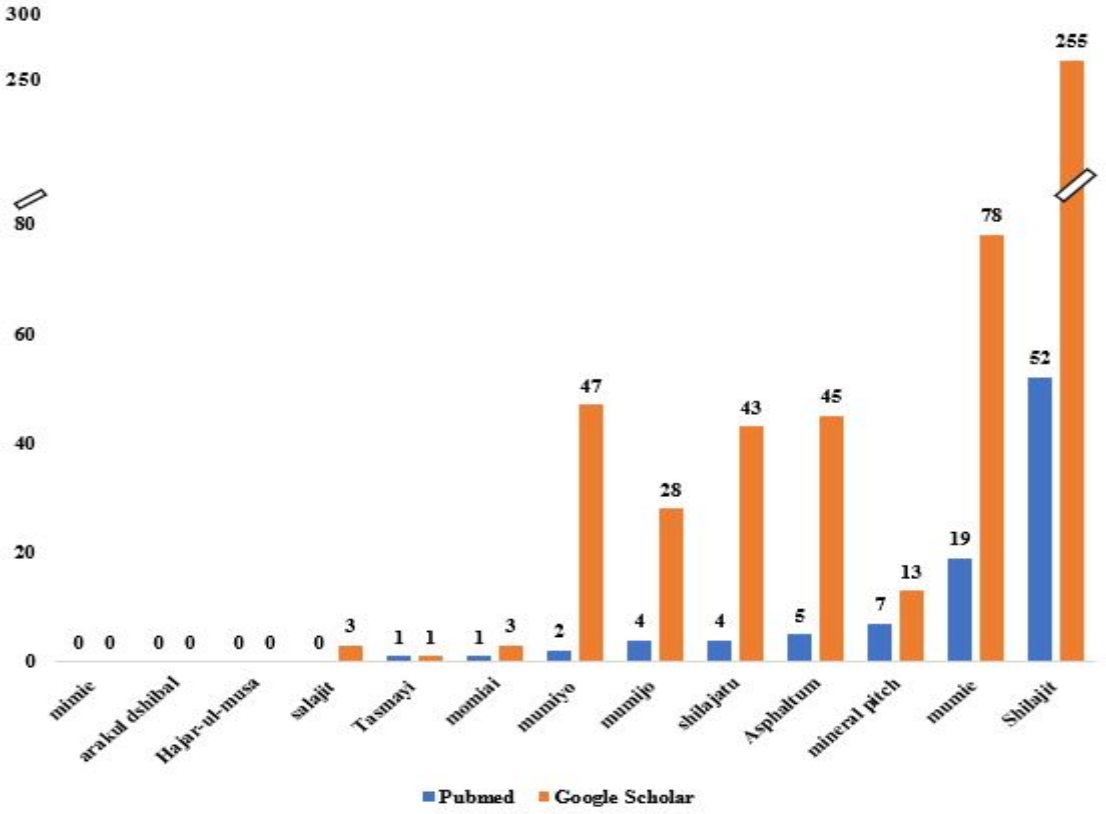

Figure 1. Shilajit with its alternative names used in publications in PubMed and Google Scholar revealed Shilajit as the most used name between 1963 and 2022**.** The number of publications for each name is shown on bars.

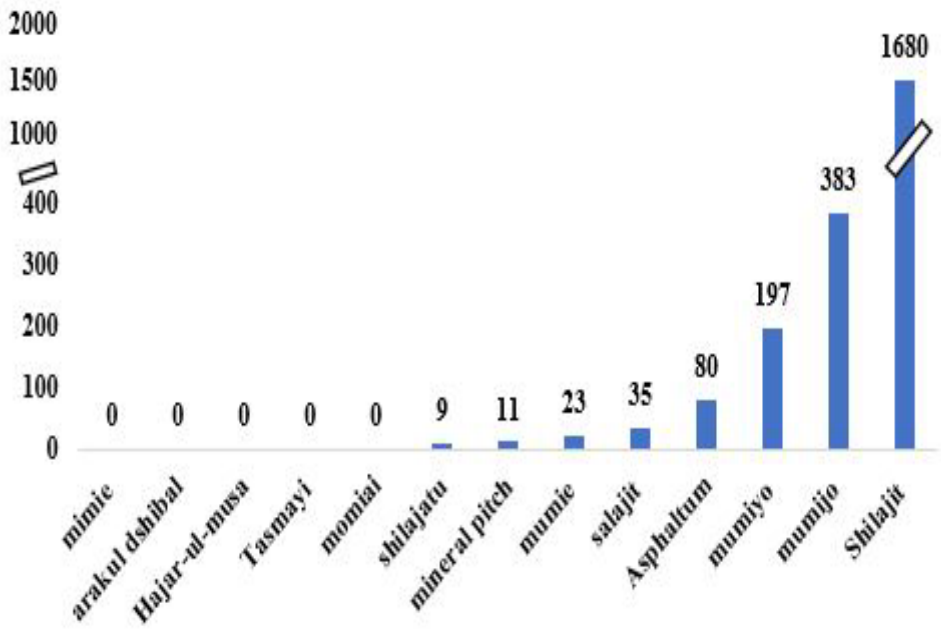

Figure 2. Shilajit with its alternative names in the description of products offered on 1-1-2023 on the online shopping site Ebay.com.

Shilajit is a black brown herbo-mineral material (Kanikkannan et al., 1995) extracted from rocks from the Himalaya mountains (C Velmurugan et al., 2012), different regions of the formerly Union of Soviet Socialist Republics, Nepal, Pakistan, Tibet, Afghanistan, and China, at altitudes of 1 to 5 kilometers (Ghosal et al., 1991; Khakimov, 1974). Shilajit is derived from Sanskrit, which means destroyer of weakness (Agarwal et al., 2007). It is a strong and very safe component, capable of managing several diseases (Carrasco-Gallardo et al., 2012). Its major pharmacological effects are attributed to its content of fulvic acid, humic acid, dibenzo-alpha-pyrones, and minerals (Mishra et al., 2019).

Shilajit is formed by the decomposition of plants by microorganisms, and it is rich in fulvic acid 60-80% (Carrasco-Gallardo et al., 2012), carotenoids (Wilson et al., 2011), potassium, calcium, and magnesium make up over 90% of the total mineral content in Shilajit, sulfur, and sodium being the next most common minerals (Trivedi et al., 2004). According to its origin, it is classified as petroleum, animal, and plant, and it could be mixed (animal feces and plants) (Ding et al., 2020; Khakimov, 1974). Shilajit acts as an anti-oxidant, and anti-inflammatory (Stohs, 2014) due to its components; humic acid, fulvic acid, and fat-soluble components such as taxol, verbenol, α-pinene; therefore, it plays an important role in the management of diabetes (Ding et al., 2020). Many varieties of shilajit differ in their composition according to the geological nature of rocks, humidity, altitude, plant species involved, and local temperature. For example, Shilajit from India-Kumaon contains 21.4% of fulvic acid, while shilajit from Nepal contains 15.4%, Pakistan 15.5%, and Russia (19%). Also, they have different percentages of humic acid and other elements (Agarwal et al., 2007). There is an increase in interest in Shilajit's properties to heal different diseases worldwide with time, which is shown by many Shilajit publications in Google Scholar and PubMed database figures (3+4).

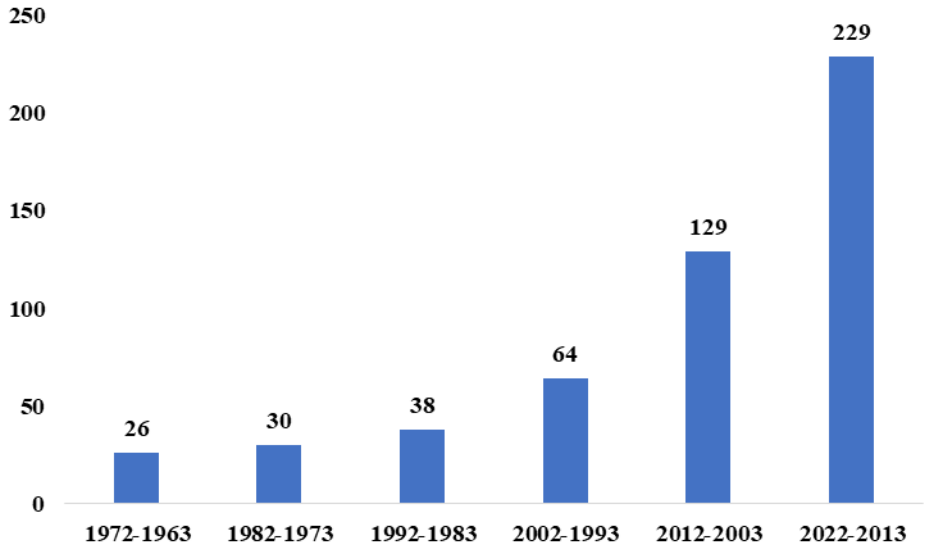

Figure 3. Increased interest in Shilajit healing properties for different diseases with time in publications in Google Scholar including academic and non-academic 516 publications between 1963 and 2022.

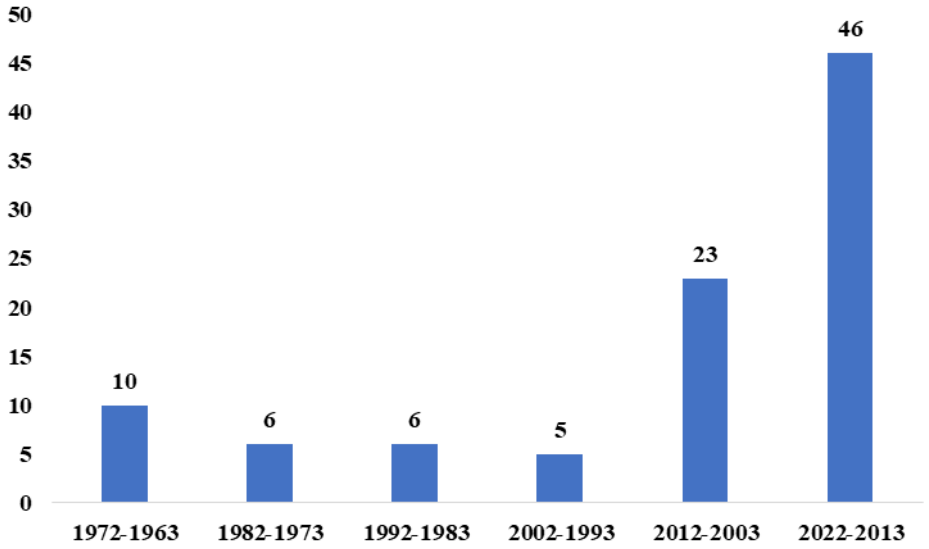

Figure 4. Increased interest in Shilajit healing properties for different diseases with time in published research papers in the PubMed database with 96 total publications between 1963-2022.

Shilajit has been used for both preventing and treating many ailments (such as diabetes, allergies, hypertension, loss of memory, immune dysfunction, arthritis, loss of libido, etc.) for more than 3000 years, indicating its powerful benefits and safety for its use in humans (Lawley et al., 2013). Diabetes involves the disruption of trace elements in the body, which can lead to increased oxidative stress, increased insulin resistance, and diabetes complications, in which Shilajit could be the richest natural product that contains these trace elements (Chandran et al., 2016). Shilajit should be used after purification and not exceed the daily recommended dose to prevent the toxicity of some molds (mycotoxins), heavy metals, polymeric quinones, and free radicals (Chopra & Chopra, 1994). Shilajit heavy metals (iron, zinc, chromium, manganese, cobalt, and lead) were determined and were at the allowed level as indicated by the World Health Organization (WHO) (Rahim et al., 2016). Purified Shilajit can be used safely in clinical research and practice (Agarwal et al., 2007; Stohs, 2014). It is used in clinical trials with 500 mg given daily for 56 days and with 1000 mg given daily for 30 days without any safety problems (Mishra et al., 2019). In another study, 20 healthy individuals received 2000 mg Shilajit capsules for 45 days without any systemic toxicity, with no significant effect on body weight, heart rate, blood pressure, glucose, urea, creatinine, uric acid, total protein albumin, and liver enzymes (Sharma et al., 2003). Shilajit safety in the long term as a dietary supplement was also revealed in animal studies, in which 24 Wistar rats (12 males and 12 females) were given 5000 mg/kg with water once daily for 91 days without any significant toxicity (C. Velmurugan et al., 2012). There are seventeen clinical trials registered in the World Health Organization on Shilajit with different diseases, three of them on diabetes between 2012-2021 without posting their results on their website (World Health Organization, 2023). In addition, there are six clinical trials registered in USA/National Institute of Health NIH/National Library of Medicine/Clinical Trials on Shilajit for different diseases, one of them on diabetes, without posting its results on their website (NIH, 2023).

Shilajit can be used commercially in many forms: resins, capsules, paste, tablets, drops, liquid, powder, oil, gummy, gel, balm, lotion, grains, and ointments. The most popular formulation offered commercially on the Ebay.com online shopping site on 1-1-2023 was resin form, as shown in figure 5.

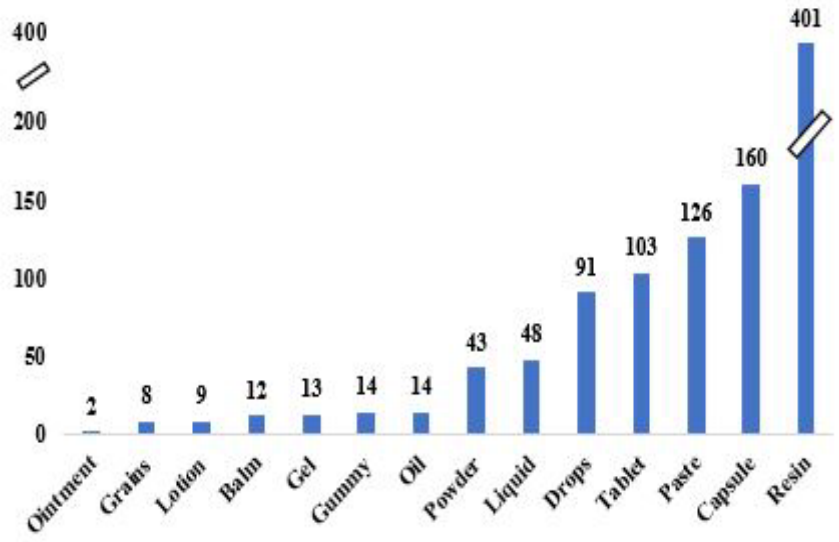

Figure 5. Different available formulations of Shilajit on Ebay.com. The most available formulation of Shilajit was the resin form offered in 1-1-2023.

4. Shilajit Studies

4.1. Shilajit studies on diabetes

Shilajit is a natural herbo-mineral product that offers a new promising approach to the long-term management of mature-onset diabetes because it appears to be beneficial and completely safe for Madhumeha treatment (type 2 diabetes mellitus) (Bihari et al., 2016). Although a variety of antidiabetic medications, such as oral hypoglycemic medications and various insulin preparations, are available for the treatment of diabetes, their long-term usage has several side effects, specifically hypoglycemia, which may lead to death. In addition, these drugs mitigate the hyperglycemia symptoms of diabetes and do not correct the underlying cause, which is the accumulation of lipids in the pancreas, liver, and muscles (Donath & Shoelson, 2011; Mirmiran et al., 2014). Besides its safety, Shilajit includes a wide range of components that reduce obesity, which is implicated in many diseases such as diabetes (Patil et al., 2022; Pattonder et al., 2011). In 2017, a clinical study of giving 500 mg of Shilajit capsule twice daily to forty-five patients for 3 months improved their hyperglycemia symptoms and significantly reduced their fasting glucose levels. There was a significant reduction in fast blood sugar and postprandial blood sugar by 24.01% and 20.23%, respectively. More than 75% of the patients had relief from polyuria, polyphagia, polydipsia, general weakness, and reduced libido (Gupta et al., 2016). In another study, 48 patients with type 2 diabetes received Vamana & Virechana (for 30 days) and 1000 mg Shilajit capsule twice a day before food with practicing Yoga for 60 days, showed that 29.1% of them improved markedly in hyperglycemia symptoms (polyuria, thirst, sweating,

constipation, tingling sensation, dyspnea, weakness, increased sleep, and appetite) with improvement in body weight, body mass index (BMI), cholesterol, LDL, triglycerides and decrease of 26-50 mg/dL in fast blood sugar (FBS) and postprandial blood sugar (PPBS). 20.8% of patients got moderate improvement in symptoms, body weight, BMI, and lipids and a decrease of 10-25 mg/dL in FBS and PPBS, and the rest were just like the control group (Raju & Sharma, 2016). Forty patients with type 2 diabetes received 250 mg Shilajit capsules twice a day for 12 weeks showed significant improvement in lipid profile, endothelial function, and cardiovascular parameters (Niranjan et al., 2016). In another study, thirty patients who received Shilajit showed a significant improvement in hyperglycemia symptoms (polyuria, polyphagia, polydipsia, weakness, FBS, PPBS) (Bihari et al., 2016). Capsules containing 250 mg of Shilajit extract and 250 mg of Ashwagandha (Withania somnifera) were administered with type 2 diabetes mellitus twice in the morning and evening to thirty-two patients significantly improved fasting blood sugar and lipid profile. Furthermore, in 18 of them (56%) hyperglycemia symptoms were improved (Upadhyay et al., 2009). In a study done in 2014, eighty-four diabetic patients, whereby a third of them received 500 mg Shilajit capsule twice a day with water after meal for three months, showed improved hyperglycemia symptoms (polyuria, polyphagia, polydipsia, weakness, cramps, loss of libido, joint pain, tingling sensation, hyperesthesia, numbness, hot and cold sensation, and burning sensation). Furthermore, Shilajit treatment significantly reduced their fasting blood sugar and postprandial sugar (Kumar et al., 2014).

Potassium, magnesium, and zinc are at lower concentrations in the skeletal muscles of diabetic patients compared to healthy controls (SJÖGREN et al., 1988). It has been shown in a clinical trial involving 7542 adults that potassium intake is inversely associated with abdominal obesity and fasting hyperglycemia (Shin et al., 2013). In another clinical trial, an increase in potassium intake in healthy individuals was involved in the increase of insulin secretion (Dluhy et al., 1972). Administration of magnesium in type 2 diabetes, improved insulin-mediated glucose uptake (Barbagallo et al., 2003). Zinc is important for the processing and storage of insulin (Chabosseau & Rutter, 2016). Chromium is an essential mineral for fat and carbohydrate metabolism. It has been shown in a recent metanalysis of 25 randomized controlled trials that consumption of chromium significantly reduced glycated hemoglobin (HbA1c), fasting blood sugar, triglycerides, and increased HDL levels (Suksomboon et al., 2014). Its deficiency led to diabetes in patients with long-term parenteral nutrition and the diabetes was resolved after chromium supplementation (Jeejeebhoy et al., 1977). Shilajit contains many trace elements including, chromium, potassium, magnesium, zinc, copper, iron, and many others (Mishra et al., 2019). Shilajit contains chromium, which is very important in carbohydrate and lipid metabolism and is recommended to be taken by diabetic patients; it increases insulin binding to its receptors; thus, it increases insulin sensitivity (Anderson, 2000). Taking a mixture of 12 herbs twice a day for 13 days in 10 diabetic patients, including Shilajit, significantly reduced the accumulative hemoglobin HbA1C (Pal & Shrivastav, 2020). In one of the studies, the chromium found in the average of two samples was approximately 0.005% (Rahim et al., 2016), in which a dose of 500 mg will contain 0.025 mg or 25 µg, which is considered adequate intake for healthy males and females (Russell et al., 2001).

In a recent study, fulvic acid in Shilajit acts as exercise; it increased metabolism, ATP consumption, and protection of mitochondrial membrane potential while decreasing insulin resistance, liver fat, and weight in high-fat diet-fed mice correcting glucose and insulin irregular levels. In the same study, fulvic acid increased ATP and glucose uptake in C2C12 muscle progenitor cells (Natsume et al., 2018). In another study in Wistar rats, Shilajit with a concentration of 200 mg/ kg was dissolved in normal saline administered orally for five weeks, showed considerable antioxidant capacity, and reduced the following: lipid levels, inflammation, and blood glucose by more than 50% compared to control, and even inhibited hemoglobin glycation better than insulin and the Glibenclamide drug (Vemuri et al., 2018). Furthermore, Shilajit prevented streptozotocin-induced degeneration of pancreatic beta cells. Diabetic albino rats received three doses of Shilajit (50, 100, 200 mg/kg/day orally), showed a significant reduction in blood glucose and a beneficial effect on the lipid profile (Trivedi et al., 2004). Giving 100 mg/kg Shilajit orally to streptozotocin-induced diabetic Wistar rats attenuated hyperglycemia, and significantly increased superoxide dismutase, which could protect the pancreatic beta cells from damage induced by oxidative stress (Bhattacharya, 1995). Injection of processed Shilajit (50 µg/Kg) simultaneously with insulin (0.25-1.0 U / kg) both subcutaneously, improved and extended the hypoglycemic effect of insulin on streptozotocin-induced diabetes in rats, while chronic administration of processed Shilajit (1.0 mg/kg twice a day intraperitoneally) prevented streptozotocin-induced diabetes in rats (Kanikkannan et al., 1995).

The underlying cause of diabetes is mainly associated with obesity, oxidative stress, and inflammation (Donath & Shoelson, 2011; Natsume et al., 2018). Shilajit has been shown to reduce all these factors involved in diabetes, which will be discussed below.

4.2. Shilajit studies on obesity

Obesity is one of the most prevalent public health problems associated with nutritional and clinical conditions; it is defined as the condition in which an excessive amount of fat is accumulated in the body (NICE & Care, 2006; Pattonder et al., 2011). Obesity can lead to insulin resistance, hypertension (Wilding et al., 2016). It is associated with a high risk of developing type 1 diabetes (Ferrara et al., 2017; Rewers & Ludvigsson, 2016), and type 2 diabetes (Verma & Hussain, 2017). Individuals with obesity and abdominal adiposity are at increased risk of hyperinsulinemia, insulin resistance, and diabetes (Warolin et al., 2014). Obesity is associated with an increased risk factor for several non-communicable diseases (Leitner et al., 2017). Recent evidence suggests that oxidative stress and inflammation may be the mechanistic link between obesity and related complications such as diabetes in obese patients, and antioxidant defenses are also lower in obese patients than their normal weight counterparts, and their levels inversely correlate with central adiposity (Gariballa et al., 2013). Obesity is also characterized by higher levels

of reactive oxygen or nitrogen species (Issa, 2016), while the first molecular link between obesity and inflammation, is the inflammatory cytokine tumor necrosis factor alpha (TNF-α), which is overexpressed in the adipose tissues (Ruan et al., 2002).

Shilajit increases metabolism and has an antioxidant effect on fat oxidation in various ways and can lower cholesterol levels in the blood (Saqib et al., 2016). Its main component, fulvic acid, contains supercharged antioxidants, superoxide dismutase, and free radical scavengers, all of which can aid fat metabolism (Narayanan & Kharkar, 2019). Fulvic acid and dibenzo-a-pyrones (DBP) present in Shilajit promotes cell division and increase metabolism (Stohs, 2014). Shilajit enhances and maintains cell function and its organelles, and also sustains cell energy by promoting ATP production (Bhattacharyya et al., 2009).

A mixture of Shilajit and Agnimantha (*Premna integrifolia*), a type of herb (250 mg), was given with warm Luke water orally twice a day before food to 32 patients for 45 days, significantly reduced obesity-accompanied signs (shortness of breath, sweating, overeating, heaviness in the body, thirsty, large abdomen, large breast, and weakness). Furthermore, this treatment was effective in reducing body weight, BMI, chest girth, abdomen girth, hip girth, mid-arm girth, and waist-to-hip ratio (Patil et al., 2022). Fifty-three obese patients were administered 500 mg capsule containing a mixture of Shilajit and Agnimantha (*Clerodendrum phlomidis* Linn.) twice a day for 10 weeks with Lukewarm water, significantly relieved signs accompanied obesity (pendulous movement of body parts, heaviness of the body, excessive perspiration, excessive thirst, bad body odor, excessive hunger, shortness of breath, lack of energy, hypersomnia, oily or greasy body, skin fold thickness, large organ measurements, and weakness). Furthermore, treatment significantly decreased BMI and weight (Pattonder et al., 2011). Seven patients received 500 mg of Shilajit capsule with 250 mg capsule of Khadir Ghana herb (*Acacia catechu*) and 500 mg of Kutaki herb capsule (*Picrorhiza kurroa*) for three months; significantly reduced their weight, BMI, waist circumference, hip circumference, and these parameters were reduced more when combined with regular exercise and a healthy diet in another 10 patients receiving the same herbs (Bhavna et al., 2013). Thirty-two diabetic patients with type 2 diabetes received a mixture of 250 mg Shilajit and 250 mg of Ashwagandha (*Withania somnifera*) twice a day for four weeks, significantly reduced cholesterol, LDL, VLDL, triglyceride, and increased HDL (Upadhyay et al., 2009). Two grams of purified Shilajit were administered to twenty normal medical students for 45 days, significantly reducing serum triglycerides, cholesterol, LDL, and VLDL, while improving HDL (Sharma et al., 2003).

Giving Shilajit of 200 mg/kg orally to streptozotocin-induced diabetic Wistar rats, significantly reduced triglyceride (TG), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL), while significantly increased high-density lipoprotein (HDL) (Vemuri et al., 2018). Ten male albino rats fed a high-fat diet containing 20% fat (hyperlipidemic rats) and received 200 mg/kg Shilajit orally for 8 weeks, significantly reduced their weight compared to the control (Saqib et al., 2016).

4.3. Shilajit studies on oxidative stress

Oxidative stress is defined as a ratio of highly reactive oxygen species (ROS) to antioxidants that is out of balance (Sies, 1997). Endogenous antioxidants such as glutathione (GSH) and superoxide dismutase (SOD) are outmatched when the cellular equilibrium swings towards greater ROS (Al-Shudiefat et al., 2013; Al-Shudiefat et al., 2022). Cellular dysfunction, lipid peroxidation, and cell death can lead to chronic inflammatory disorders that are associated with oxidative stress. It induces the synthesis of inflammatory mediators, which in turn increases the formation of reactive oxygen species (Giacco & Brownlee, 2010) and plays a key role in the progression of diabetes complications (Mathebula, 2018). Oxidative stress and activation of the JNK pathway are involved in the damage of pancreatic beta cells and therefore the etiology of type 1 and type 2 diabetes (Kaneto et al., 2007). Some of the consequences of oxidative stress are insulin resistance, beta-cell dysfunction, impaired glucose intolerance, and mitochondrial dysfunction which could lead to diabetes disease. Furthermore, oxidative stress can arise from lifestyle, disease, sleep deprivation, and high caloric intake (Rains & Jain, 2011).

Diabetes mellitus can contribute to increasing oxidative stress through the polyol pathway. The polyol pathway is based on a family of aldo-keto reductases that can use a wide range of carbonyl compounds as substrates and reduce them using nicotinic acid adenine dinucleotide phosphate (NADPH) to each other's sugar alcohols (polyols) (Yan, 2018). The enzyme aldose reductase converts glucose to sorbitol, which is then oxidized to fructose by the enzyme sorbitol dehydrogenase (SDH) with NAD as a cofactor (Mathebula, 2018). The original conversion of glucose to sorbitol leads to lower levels of NADPH, which is required as a cofactor for glutathione reductase to keep the levels of reduced glutathione (GSH), a key cellular antioxidant, within safe limits (Yan, 2018). Decreased GSH levels can lead to an increase in reactive oxygen species, which can contribute to oxidative stress (Jawaid et al., 2020). Fulvic acid coming from the humic substance of Shilajit helps in reducing free radicals which can protect the pancreatic beta cells that produce insulin from damage (Bastaki, 2005).

Sixty postmenopausal women received 500 mg of Shilajit extract for 48 weeks, significantly decreased oxidative stress (decreased malondialdehyde (MDA)), and significantly increased glutathione compared to placebo (Pingali & Nutalapati, 2022). Sixty-one diabetic patients received 500 mg Shilajit capsules twice a day for 30 days, significantly decreased oxidative stress (decrease in malondialdehyde), and significantly increased catalase (Saxena et al., 2003). Twenty normal volunteers received 2 grams of Shilajit for 45 days, significantly increased superoxide dismutase, vitamin E, and vitamin C (Sharma et al., 2003).

Shilajit administered at a dose of 800 mg/kg in Sprague Dawley rats for two weeks, significantly increased glutathione, glutathione peroxidase, catalase, and superoxide dismutase, while significantly decreased oxidative stress (MDA) (Derhami et al., 2022). Shilajit 250 mg/kg administration to Wistar rats ameliorated acetaminophen, increased hepatic damage parameters including alanine amino transferase, aspartate aminotransferase, gamma glutamine transferase, nitric

oxide, oxidative stress, and it significantly improved glutathione peroxidase (Atashbar et al., 2018). Shilajit increased total antioxidant capacity by 97%, superoxide radical scavenging activity, and hydroxyl radical scavenging activity, whereas, it inhibited streptozotocin-induced hemoglobin glycation in Wistar rats (Vemuri et al., 2018). Rats received processed Shilajit 50 mg/kg i.p. for 21 days, led to an increase of superoxide dismutase, catalase, and glutathione peroxidase in the frontal cortex and striatum and prevented methyl methacrylate-induced oxidative stress (Bhattacharya et al., 1995).

4.4. Shilajit studies on inflammation

Lipid accumulation, inflammation, and diabetes are intricately linked, and a growing body of evidence suggests that inflammation plays a critical role in the pathogenesis of type 2 diabetes. Lipid accumulation, particularly in adipose tissue and the liver, can trigger an inflammatory response that can contribute to the development of insulin resistance and ultimately lead to the onset of diabetes (Hotamisligil, 2017).

Adipose tissue is a key site for lipid accumulation in the body, and obesity is associated with chronic low-grade inflammation of adipose tissue, characterized by the infiltration of immune cells such as macrophages (Gregor & Hotamisligil, 2011). These immune cells produce pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), which can activate inflammatory pathways such as the nuclear factor-kappa B (NF-κB) pathway, ultimately leading to the production of more cytokines and the recruitment of more immune cells (Shoelson, 2006). The chronic low-grade inflammation that accompanies lipid accumulation can promote insulin resistance by impairing insulin signaling and promoting the breakdown of insulin-sensitive tissues. Furthermore, inflammation can interfere with the normal functioning of adipose tissue, resulting in the release of free fatty acids into the bloodstream and the accumulation of toxic lipid metabolites in organs such as the liver, muscle, and pancreas, all of which can further exacerbate insulin resistance and ultimately lead to the onset of diabetes (Tilg & Moschen, 2008).

Several lines of evidence support the role of inflammation in the development of insulin resistance and diabetes. For example, in a study of obese and non-obese individuals, the obese group had higher levels of pro-inflammatory cytokines such as IL-6 and C-reactive protein (CRP), which were positively correlated with insulin resistance (Kern et al., 2001).

Inflammation has been shown to play an important role in the pathogenesis of diabetes through IKKβ pathway, since inhibition of this pathway by giving sodium salicylate and aspirin, which are used in rheumatic fever and rheumatoid arthritis as anti-inflammatory agents, can reverse insulin resistance and decrease hyperglycemia (Yuan et al., 2001). This was proved by administering aspirin 7 g/day to nine patients with type 2 diabetes for two weeks, which resulted in a decrease in fasting plasma, triglycerides, total cholesterol, and C-reactive protein (an indicator of inflammation) and insulin clearance (Hundal et al., 2002). In type 1 diabetes mellitus, beta cells are suggested to fail due to the response to inflammatory apoptosis resulting from the secretion of IFN-gamma controlled by the PTPN2 gene (Moore et al., 2009). Inflammatory cytokines such as IL-6 have been shown to stimulate apoptosis in beta-pancreatic cells and act as a predictor of the progression of type 2 diabetes (Pradhan et al., 2001). There is a link between the inflammatory TNF-alpha cytokine and insulin resistance, obesity, and beta cell inflammation, and its overexpression led to beta cell death and insulin resistance (Pradhan et al., 2001; Ruan et al., 2002).

Sixty postmenopausal women received 500 mg of Shilajit for 48 weeks, significantly decreased the inflammatory protein hsCRP (Pingali & Nutalapati, 2022). Shilajit was shown to protect against acetaminophen-induced liver injury in rats and significantly reduced the inflammatory cytokines IL-6, IL-1β and TNF-α (Firozsalari et al.). Shilajit administered at a dose of 200 mg/kg.bw to streptozotocin-induced diabetic rats, reduced the expression of inducible nitric oxide synthase (iNOS) proinflammatory gene in pancreatic tissue (Vemuri et al., 2018). Oxidative stress and inflammation are implicated in the pathogenesis of obesity (Savini et al., 2013). Oxidative stress stimulates the production of inflammatory mediators (Pattonder et al., 2011), while fulvic acid decreases proinflammatory markers (Giacco & Brownlee, 2010). Fulvic acid could prevent chronic inflammatory diseases, including diabetes, by reducing the release of proinflammatory mediators from cells (Koya et al., 2003). Fulvic acid acts as an immune modulator and influences the redox state (Sharma et al., 2003). Shilajit at a concentration of 50 mg/kg i.p. showed significant anti-inflammatory effects against carrageenan-induced pedal edema in rats (Goel et al., 1990).

In summary, Shilajit can reduce the risk factors (obesity, insulin resistance, inflammation, oxidative stress) that can lead to diabetes in normal people, while at the same time, it could reverse or ameliorate type 2 diabetes mellitus and prevent its progression to fatal complications, as shown in figure (6).

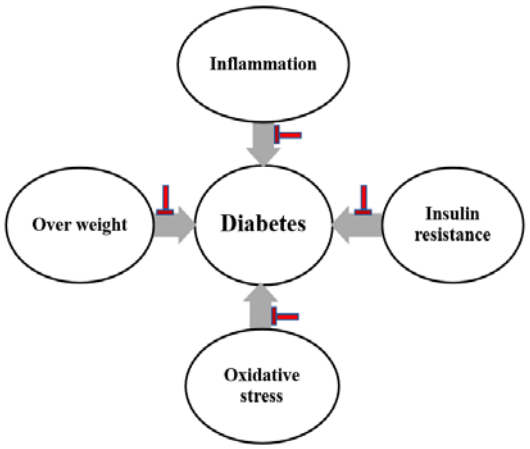

Figure 6. Possible mechanisms by which Shilajit could prevent, reverse diabetes, or ameliorate its symptoms and its complications.

4.5. Shilajit studies on other diseases and conditions

In addition to Shilajit benefits for diabetes (Gupta et al., 2016; Raju & Sharma, 2016), it can also be beneficial for other diseases and conditions, including insulin resistance (Gupta, 1966; Kanikkannan et al., 1995), obesity (Patil et al., 2022; Pattonder et al., 2011), inflammation (Firozsalari et al.; Pingali & Nutalapati, 2022), oxidative stress

(Atashbar et al., 2018; Derhami et al., 2022), arthritis (Azizi et al., 2018; Lawley et al., 2013), cancer (Kloskowski et al., 2021; Pant et al., 2012), bone health (Cesur et al., 2019; Labban, 2013), allergy (Ghosal et al., 1989; Sadeghi et al., 2020), mental health (Jaiswal & Bhattacharya, 1992; Khaksari et al., 2013), immune system (Bižanov et al., 2012; Musthafa et al., 2018), increased energy (Bhattacharyya et al., 2009; Stohs et al., 2017), adaptogenic (Agarwal et al., 2007; Bansal & Banerjee, 2016), antiaging and rejuvenating (Ghosal, 1990; Wilson et al., 2011), and for sexual health (Ikram-ul-Haq et al., 2016; NİZAM & SELÇUK, 2021). These benefits are shown in table 2.

Table 2. Some diseases/ conditions in which Shilajit used.

Diseases/conditions	Research Reference/(s)
Diabetes	(Gupta et al., 2016; Raju & Sharma, 2016)
Insulin resistance	(Ghezelbash et al., 2022; Kanikkannan et al., 1995)
Obesity	(Patil et al., 2022; Pattonder et al., 2011)
Inflammation	(Firozsalari et al.; Pingali & Nutalapati, 2022)
Oxidative stress	(Atashbar et al., 2018; Derhami et al., 2022)
Arthritis	(Azizi et al., 2018; Lawley et al., 2013)
Cancer	(Kloskowski et al., 2021; Pant et al., 2012)
Bone health	(Cesur et al., 2019; Labban, 2013)
Allergy	(Ghosal et al., 1989)
Mental health	(Jaiswal & Bhattacharya, 1992)
Immune system	(Bižanov et al., 2012; Musthafa et al., 2018)
Increase Energy	(Bhattacharyya et al., 2009; Stohs et al., 2017)
Adaptogenic (adapt to stress)	(Agarwal et al., 2007; Bansal & Banerjee, 2016)
Anti-aging and rejuvenator	(Ghosal, 1990; Wilson et al., 2011)
Sexual health	(Ikram-ul-Haq et al., 2016; NİZAM & SELÇUK, 2021)

* Please note that studies include animals and humans

5. Discussion

Diabetes is a major problem worldwide with high mortality and morbidity rates. Although there are many medications developed for the management of diabetes, they have many side effects, and the most common one is hypoglycemia which could be life-threatening. Some diabetes medications' side effects are shown in table 1. In addition to their side effects, these medications only treat hypoglycemia symptoms and do not address the root cause of diabetes, which is obesity and the accumulation of lipids in vital organs such as the pancreas, liver, and muscles (Donath & Shoelson, 2011; Natsume et al., 2018). Therefore, there is a need for a natural remedy for diabetes, which is safe for the long term and with fewer side effects. Shilajit is a natural exudate that occurs by the decomposition of residues of plants and animals in high-altitude rock mountains and has been used for thousands of years in traditional medicine for several diseases including diabetes (Lawley et al., 2013). Furthermore, several studies in humans and animals revealed its safety as a nutritional supplement for a long period (Mishra et al., 2019). There is an increase in interest in Shilajit research and in the commercial use of it for different diseases over time, which is obvious form the number of publications in Google Scholar, the PubMed database, and the Shilajit products offered in E-bay.com figures (1-4). For commercial use, we first looked at three big online companies including www.E-bay.com, www.Amazon.com, and www.Alibaba.com; because they are large online retailers, and it was easy to search for certain products on their websites. Because the products of Shilajit offered were the largest on E-bay.com compared to the other two companies, we decided to use E-bay website to reveal people interest in Shilajit products. Commercially, Shilajit is used in many formulations, in which resin is the most formulation offered in Ebay as shown in figure 5.

It is suggested that Shilajit's antidiabetic activity is through increasing numbers of beta cells in the pancreas (Gupta, 1966), increasing insulin sensitivity, increasing metabolism, or could be through decreasing hyperglycemia, obesity, oxidative stress, and inflammation (Natsume et al., 2018; Winkler & Ghosh, 2018), Therefore, Shilajit can reverse, heal, and ameliorate diabetes root cause (Figure 6). Moreover, Shilajit contains chromium and can decrease the glycation of hemoglobin, which is important for combatting diabetes (Jeejeebhoy et al., 1977; Pal & Shrivastav, 2020). Besides that, fulvic acid of Shilajit acts as exercise by increasing metabolism and ATP consumption, and protecting mitochondrial membrane potential, which is important for correcting levels of insulin and glucose in the blood (Natsume et al., 2018). Shilajit also acts as an exercise by increasing metabolism, and it contains minerals essential for glucose metabolism such as chromium. Shilajit is used for other conditions other than diabetes; it is used for insulin resistance, obesity, inflammation, oxidative stress, arthritis, cancer, allergy, mental health, immune system, increased energy, adaptogenic, antiaging, and for sexual health as shown in (table 2).

The most challenging part of this investigation was that Shilajit has more than twenty names according to different languages (Wilson et al., 2011), and we searched for the most popular names to obtain this review. Another difficulty was that one of the Shilajit names (mumie) had the meaning of mummy in some languages and other languages means mom; therefore, translation of different articles was a big obstacle and to filtrate these results manually was a big headache. We also faced some difficulties dealing with some Ayurvedic (using natural products as medicine) terms that have either Sanskrit or Hindi language origin regarding herbs and symptoms in Indian Shilajit publications.

6. Conclusions

Although there are many medications used for diabetes mellitus, they have many side effects; the most common one is hypoglycemia which could threaten life. In addition, they are not addressing the root cause of diabetes, which is obesity. Shilajit is a natural product that is proved to be safe with fewer side effects and with anti-hyperglycemic, anti-obesity, anti-oxidative stress, and anti-inflammatory effects that may reverse or ameliorate diabetes and its

complications. Therefore, Shilajit could be used as an alternative to anti-diabetic drugs, which have some negative side effects. Moreover, Shilajit acts as an exercise effect by increasing metabolism, and it contains minerals important for glucose metabolism such as chromium, potassium, magnesium, and zinc. Furthermore, Shilajit is used for many diseases and conditions other than diabetes such as insulin resistance, obesity, inflammation, bone health, Allergy, mental health, immune system, increase energy, adaptogenic, antiaging, rejuvenator, and for sexual health, and many others.

Since the current Shilajit research on diabetes has promising results, more animals and clinical trials are warranted to explore Shilajit mechanisms and benefits in diabetic patients. From these studies, exact recommendations on the doses that could be taken for patients within the permissible level could be achieved with the most beneficial outcomes.

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The authors declare no conflict of interest.

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