Antioxidant and anti-proliferative effect of overnight soaked water extract of fenugreek

(*trigonella foenum-graecum*) seeds

Mousumi Ghatak*[1] Pramod Kumar Singh[*1]

[*1]Netaji Subhas University, Jamshedpur, Jharkhand, India

Affiliation: Research Guide and Head, Netaji Subhas University, Jamshedpur, Jharkhand

Abstract:

Fenugreek has been the subject of clinical trials in recent years as a potential nutraceutical. Fenugreek plants have been demonstrated to have immunomodulatory, hypocholesterolaemic, hypoglycaemic, gastro- and hepatoprotective. Pharmacological properties of fenugreek have been investigated in order to determine the role in diabetes management and cardiovascular health is due to the presence of bioactive compounds that may be responsible for such a novel work. In this research, we evaluated the presence of phytochemicals and their antioxidant activity.

Introduction:

Around 80% of people around the world, particularly in underdeveloped nations, still rely on medicinal plants to treat and enhance their general health (Kambojet al., 2000). This is primarily owing to the widespread perception that plant-derived medications have no negative effects, are inexpensive, and are readily available locally (Gupta and Raina, 1998). According to a survey published by the World Health Organization (WHO), herbal therapies are used two to three times more than conventional medicines around the world (Evans, 1990). Fenugreek (*Trigonella foenum-graecum* L.) is a dicotyledonous annual crop of to the *Fabaceae* family (subfamily *Papilionaceae*). *Trigonella* means triangle, possibly due to the triangular shape of its blossoms, and *foenum graecum* means "Greek hay," implying its use as a feed crop in the past (Petropoulos, 2002). Fenugreek has also been utilised as a medicinal plant in various regions of the world for over two thousand years. Fenugreek has been used in Indian Ayurvedic and Traditional Chinese Medicines for centuries, where it is used as a galactogogue or lactation stimulant in women after childbirth, as well as for treating wounds and tired muscles (Thirunavukkarasu, 2003).

Herbs and spices have long been used to improve the flavour. It has been used to increase the flavouring and colour, and also modifies the texture of food materials. However, the bioactive phenolic content of these plant-based products is currently attracting interest. In order to establish the phenolic profiles accurate quantification of major phenolics was performed by multiple reactions monitoring in a triple quadrupole mass spectrometer. (Vallverdú et al., 2014).

Materials and Methods:

Fenugreek seeds were procured from local market of Jamshedpur, Jharkhand. Seeds were soaked in water in the ratio of (1:10) overnight. On next day extract were filtered and stored in freeze at 4ºC.

Methods:

Qualitative analysis of phytochemicals was done using the methods of (Soetan, 2008). Antioxidant activity of different phytochemicals was done using the methods of (Liangi et al., 2002 and Hitoshi et al., 2004). Antibacterial activity was done using MIC inhibition.

Results:

The aqueous extract of fenugreek seeds contained a significant level of these phytochemicals in the current investigation. All of the phytochemicals investigated in this study have been shown to have antioxidant activity and are therefore helpful to humans. The extract contains a high amount of tannins, phenolics, flavonoids, and alkaloids, whereas carbohydrates, glycosides, coumarin, and quinine are present in less amounts. Phytochemical ingredients found in samples are recognised to be biologically active chemicals with antibacterial, antioxidant, antifungal, anticancer, and antidiabetic properties (Soetan, 2008).

Sample	Presence/Absence
Steroids	+++++
Phenols	+++++
Saponins	+++++
Alkaloids	+++++
Glycosidic	+++++
Tannins	+++++
Flavanoids	++
Coumarin	+++++
Quinone	+++

Table 1. Qualitative test of Phytochemicals.

Antimicrobial test:

Fenugreek seeds contain a wide spectrum of phytochemicals as shown in the above table. The extract had high levels of alkaloids, flavonoids, saponins, terpenoids, and tannins. These are all the types of plant secondary metabolites that are most typically found in plants and have been shown to have a positive impact on plant defence. (Soetan, 2008). The fluctuation in phytochemical levels could be caused by a variety of variables. They could be affected by factors such as location, season, and extraction process. Phytochemical synthesis and accumulation are influenced by species, age, season, and environmental conditions, according to Ezeabara & Egwuoba (2016). Plant organs such as fruits, flowers, leaves, stems, and roots acquire phytochemicals. Flavonoids (Crozier et al; 2006) and alkaloids (Zulak et al., 2006) serve a defence role in the plant against herbivores and diseases. The results of phytochemical antibacterial activity are shown in the table below.

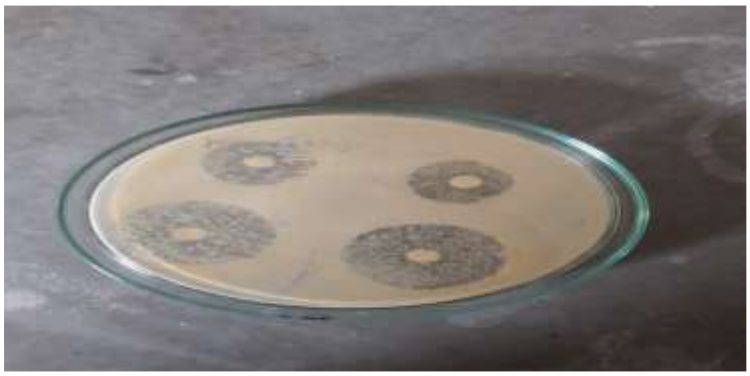

Fig 1. MIC of Plant phytochemicals

The sensitivity tests of aqueous extract reveal that bacterial strains have a beneficial effect, with variable diameters depending on the dose. The *E. coli* strain's inhibitory zone measured 17 mm when the extract concentration was 25 mg/ml, 22 mm when the concentration was 50 mg/ml, and 28 mm when the concentration was 100 mg/ml. The widths of inhibitory zones are found to be proportional to the concentration of crude extracts. The major substances involved in antioxidant action are phenolics, which are found in plant photochemicals. (Soetan, 2008).

Antioxidants activity:

An antioxidant is a chemical that prevents other molecules from oxidising. Although oxidation reactions are necessary for life, they can also be harmful. The highly reactive substances formed in the body as by-products of regular processes or those that enter the body from the environment are released by free radicals produced during oxidative processes. Oxidative stress is caused by a lack of antioxidants or inhibition of antioxidant enzymes, which can damage or destroy DNA cells. Anti-oxidants are substances that prevent oxidative damage to cells and bodily tissues by inactivating oxygen species/free radicals. Plant foods provide multiple health benefits by maintaining a balance between oxidants and antioxidants in the body, which helps to prevent oxidative stress. Glutathione, vitamin C, vitamin A, and vitamin E are just a few of the nutrient/non-nutrient antioxidants found in plant/animal meals. Antioxidants are extensively utilised as dietary supplements, and their effectiveness in preventing diseases including cancer, coronary heart disease, and even altitude sickness has been studied. The antioxidant activity of the extracts was measured as a percentage of DPPH radical scavenging activity, with higher values indicating more antioxidant activity. The extract has a 54 percent antioxidant activity, with the maximum activity. (table 2). There is a good linear association between the aqueous extract and DPPH radical scavenging in our results. These findings suggested that the radical scavenging potential of seed aqueous extracts is mostly determined by their phytochemical content.

Samples	DPPH (%) Inhibition
100 µl	54%

Table 2. DPPH Inhibition

Discussion:

The purpose of this study is to evaluate the biological activities of fenugreek seeds soaked overnight in water. On evaluating the aqueous extract, it is found that extracts have better antioxidant and

antibacterial activities. Furthermore, this study provides the home made remedy for numerous degenerative diseases. The aqueous extract is now considered to be the best extracting solvent for recovering powerful antioxidant components from fenugreek, employing that the related extracts had a promising potential for the isolation of natural antioxidant and antibacterial compounds. Furthermore, the results presented would undoubtedly aid in determining the potency of the examined fenugreek sections, particularly the seed extract, for medical health functions as well as functional food and nutraceutical uses. The bioactive chemicals in fenugreek have been demonstrated to have antidiabetic, antifertility, anticancer, antibacterial, antiparasitic, lactation stimulant, and hypocholesterolemic properties, according to the literature. According to the findings of the current investigation, the water extract has the capacity to kill hazardous pathogenic microorganisms. As a result, fenugreek may be a valuable source of physiologically active chemicals for the development of new antibacterial medications. The pharmacological action of these phytochemicals identified in fenugreek extract is investigated in this study.

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Conflict of Interest: Authors have no any conflict of interest.

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EVALUATION OF DNA DAMAGE AND MECHANISM OF REPAIR IN TYPE 2 DIABETES MELLITUS.

Mousumi Ghatak[1], Pramod Kumar Singh[2]*
[1]Research scholar, Dept. of Zoology, Netaji Subhas University
[2*]Associate Professor, Dept. of Zoology, Netaji Subhas University
*Corresponding Author: pramod@nsuniv.ac.in

Abstract:
Type 2 diabetes mellitus (T2DM) and its consequences may be linked to DNA damage, mostly through oxidative stress. It is unclear how DNA repair issues may be affecting the overall level of DNA damage in T2DM, which may be linked to genomic instability leading to cancer.The alkaline single cell gel electrophoresis (comet assay) was used to assess the degree of DNA damage and oxidative stress in Type 2 diabetes mellitus (T2DM) Wistar mice.In Diabetes induced animals there were higher levels of baseline endogenous and oxidative DNA damage than did control animals. The amount of alkylative DNA was the same in both theexperimental animals and the controls.Compared to healthy controls, diabetes animals showed increased sensitivity to the DNA damage caused by streptozotocin induced diabetes mellitus. Our findings imply that type 2 diabetes mellitus may be linked to increased levels of oxidative DNA damage, greater vulnerability to mutagens, and lower DNA repair effectiveness. These characteristics could be factors in the association between diabetes and cancer, and measurements of DNA damage and repair, as determined by the comet test, could be indicators of the likelihood of developing cancer in people with diabetes.
Keywords: Type 2 diabetes mellitus; DNA damage, Cancer; Comet assay

Introduction:
Type 2 diabetes mellitus (T2DM) can be brought on by an increased level of oxidative stress, which is brought on by hyperglycemia through activation of the sorbitol system and glycoxidation as well as by a restriction of the hexose monophosphate shunt, which reduces glutathione synthesis [1-4].Patients with inadequate glycemic control can clearly see this [5]. Reactive oxygen species (ROS), which are an accumulation of the byproducts of oxidative stress, can harm biological macromolecules like proteins, lipids, and DNA. Patients with diabetes may have weakened antioxidant defenses, including lower antioxidant levels and activity of superoxide dismutase, catalase, and glutathione peroxidase. As a result, individuals may be more susceptible to oxidative stress-related illnesses, such as atherosclerosis, the most serious complication of diabetes and the leading cause of early mortality [6, 7].Diabetes is associated with the most often observed DNA damage, 8-hydroxy-2-deoxyguanosine (8OHdG) [8]. It can be produced by a number of different ROS, such as hydroxyl radicals, singlet oxygen, peroxyl radicals, and peroxynitrite, ONOO, which can cause strand breaks, among other DNA damage and alterations to the DNA bases [9,10]. Clinical indicators and certain DNA damage in diabetes may be associated [11].

Diabetes mellitus and cancer risk may be related, according to epidemiological statistics, although the mechanism behind this link is unclear [12–14]. Hyperinsulinemia and hyperglycemia may negatively affect proliferative activity in postmenopausal women, most likely promoting the production of transforming growth factor beta [12].A greater level of glycosylated haemoglobin, a higher body mass index, and the use of medicine to manage diabetes are all associated with colorectal cancer [13].

Perturbation in glucose and insulin control may also influence colorectal carcinogenesis. The role of insulin and insulin-like growth factors, which are key drivers of proliferation and apoptosis, may also be taken into account when examining the potential relationship between diabetes and cancer [14]. These parameters may be altered in numerous animal models to affect colon cancer genesis. High insulin and insulin-like growth factor levels have also been linked by human research to a higher risk of colorectal cancer.Additionally, eating habits that promote insulin resistance or secretion, such as eating a lot of sugar, having a high glycaemic index, and consuming a lot of saturated fats, may raise your chance of developing colon cancer [14].The effect of diabetes on the prognosis of cancer patients is yet another issue. Increasing evidence suggests that diabetes may be linked to a greater mortality and cancer recurrence rate, which may make cancer that also, coexists with diabetes more likely to advance quickly and therefore more challenging to treat [15–17].

In the present work we tried to evaluate the extent of DNA damage and their repair through the aqueous extract of oyster mushroom.

Material and methods:

Male Wistar strains of rats, weighing about 150–200 g were used in the experiments.

Division and distribution of animal:

All 32 male Wistar rats were divided into 4 groups, containing 8 animals each. The division of groups was as follows:

Group 1: Normal control (NC), n= 8 Group 2: Diabetic control (DC), n= 8

Group 3: Diabetic rats treated with aqueous extract of mushroom extract, n= 8

Group 4: Diabetic rats treated with allopathic drug, glibenclamide, n=8

Methods:

2ml of fresh whole blood in collected in the tube and detect with 1:5 RBC lysisbuffer. Centrifuge at 3000rpm for 10 min, the supernatant is discarded to getlymphocytes; isolated lymphocytes are suspended in 1ml PBS.

↓

Two solutions 1% normal melting agarose (NMA) and .7% low melting agar (LMA) were prepared in PBS.

↓

Frosted microscopic slides were first prepared with 1% NMA covered immediatelywith a layer. Large cover slip and kept at 4c until the agarose had solidified.

↓

After the removal of cover slip mixture of LMA and cell suspension were rapidly added on top of the 1st agarose layer and allowed to solidify.

↓

Finally a third layer of .7% NMA was added the slides were emerged in precooled freshly prepared lysis buffer for 30min .in the dark to lyse the cell. Afterlysis the slides were placed in a horizontal electrophoresis and until filled with freshly prepared chilled electrophoresis buffer for 30min.After

30min electrophoresis was conducted on dark for 30min and 25volt.

↓

Subsequently the slides were washed with the neutralizing buffer.

↓

Just before visualization each slides was stained with ethidium bromide (EtBr) (20ug/ml).rinsed with water and covered with a cover slip.

↓

The slides were examined under fluorescence microscope. The length of the comet test was taken as a measure of DNA damage.

Results and Discussion:

The comet assay was performed by taking fresh blood from the animals of each group in order tomeasure the degree of DNA damage in diabetic animals and also to measure the degree ofrecovery in animals of treated groups. Comets with long tails were clearly observed in case ofdiabetic control group animals which indicated the DNA damage due to the oxidative stresscaused by streptozotocin (Fig: A) whereas in normal animals there was no such cometsobserved (Fig: B) The normal control group had circular nucleus indicating lack of DNAdamage. In treated diabetic group, the lesser number of comets wereobserved with shorter tail length as compared to diabetic control group. Comets with long tails were clearly observed in case of diabetic control group animals which indicated the DNA damage due to the oxidative stress caused by streptozotocin (Fig: A) whereas in normal animals there was no such comets observed (Fig: B). In aqueous extract treated diabetic group (Fig: c) the number of comets in the slide were observedwith shorter tail length as compared to diabetic control group.Recovery to the DNA damage in thetreated group animals and the recovery to the DNA damage is more in oyster mushroom extract and glibenclamide treated animals than that of the animals of other treated group.

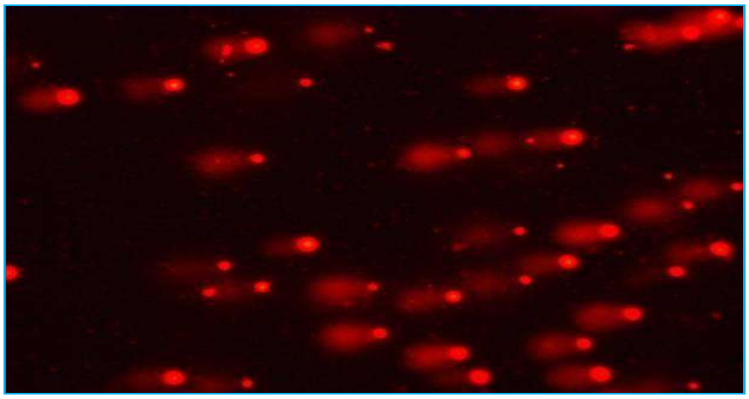

Figure A: DNA damage in Diabetic Group of animals.

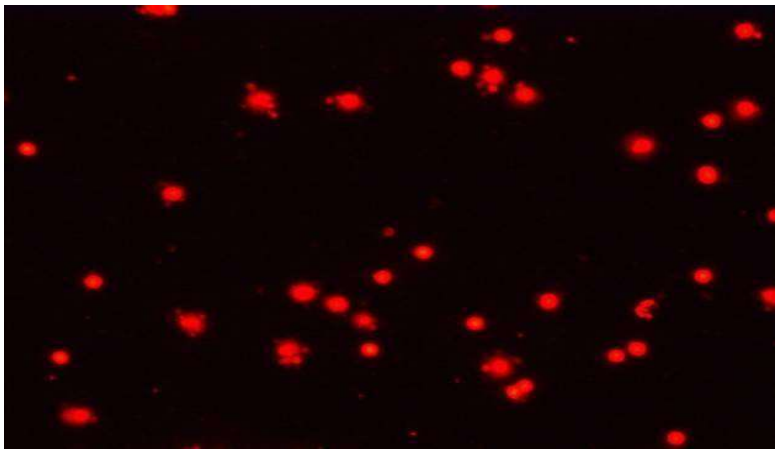

Figure B: Comets in Normal animals

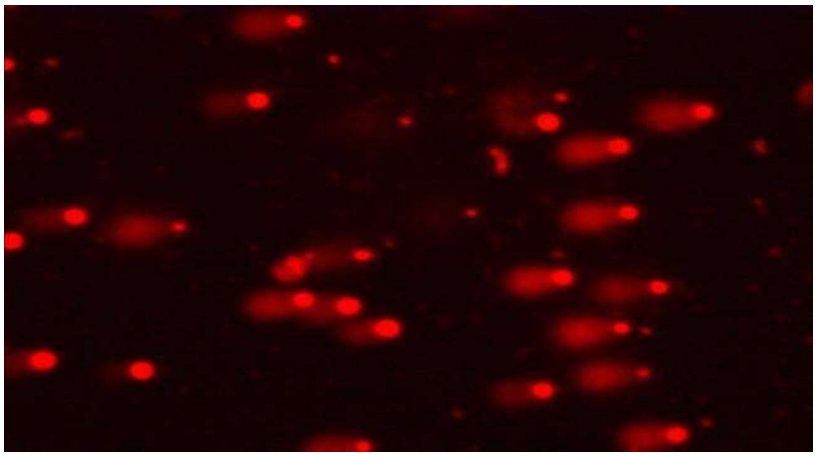

Figure C: Effect of Oyster mushroom treatment on DNA damage induced by Streptozotocin

Conclusion:

Being overweight, atherosclerosis, retinopathy, nephropathy, and other consequences are all possible with type 2 diabetes mellitus, a complex condition. There is mounting evidence that diabetes and cancer may be related. This connection may relate to the development or outward manifestation of cancer. In the current study, we looked at whether T2DM patients' mutagen sensitivity and DNA repair effectiveness differed from those of non-diabetics.We also assessed the degree of DNA damage caused by alkylation, oxidation, and base damage in each of these groups. Together, these investigations were designed to provide light on the following basic question: Does diabetes' link with cancer result from cellular reactions to DNA damage?Our findings concur with others that demonstrate elevated levels of DNA damage in diabetic patients' blood cells. However, other information suggests there is no correlation between diabetes and a higher level of DNA damage. For at least three reasons, it is advised to exercise caution when interpreting any of these findings.First off, diabetes is a condition that may involve a variety of abnormalities, some of which can be challenging to identify and whose effects on DNA are unknown. Second, type 1 and type 2 diabetes mellitus are viewed as distinct diseases, and both types of diabetes can have different processes underlying the induction of DNA damage. Glycaemic control appears to be involved in this process.Another issue arises in the case of 2DM due to the disease's age-onset. It occasionally happens in people who are significantly older than 50, an age that is frequently

linked to a wide range of physiological abnormalities and may typically be linked with a progressive deterioration of DNA repair. Both 2DM patients and controls, which ought to be age-matched, are affected by this. Third, depending on whether the cells are mononuclear or polymorphonuclear, diabetes patients' leukocytes may be differently sensitive to oxidative DNA damage.Our findings imply that T2DM may be linked to increased levels of oxidative DNA damage as well as increased vulnerability to mutagens and diminished DNA repair effectiveness. Observed vulnerability in diabetes individuals may, of course, be influenced by DNA repair itself, but additional factors may also be at play.Additionally, the existence of tiny molecules that scavenge free radicals, such as ascorbate, vitamin E, and glutathion, has a significant impact on how the cell responds to external mutagens. Our research did not examine these two components of antioxidant protection, and we believe that it should be pursued while taking these two factors into consideration. In our study, we concentrated on DNA repair, and we do think that the sluggish DNA repair rate in diabetic cells may be an indication of a general lack of antioxidant defense. Our findings imply that a panel of risk factors for diabetes-related cancer may include measurements of the degree of endogenous DNA damage, susceptibility to exogenous mutagens, and the effectiveness of DNA repair using the comet assay. The aqueous extract of mushroom is effective treatment against DNA damage,

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COMPARATIVE STUDY OF WATER SAMPLES OF TWO DIFFERENT REGIONS IN JAMSHEDPUR

Dr. Pramod Kumar Singh*, Mousumi Ghatak, Kapura Murmu, Kanchan Nag, Puja Kumari, Surupa Mukherjee, Aanchal Chaurasia

Netaji Subhas University, Jharkhand India.

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***Corresponding Author**
Dr. Pramod Kumar Singh
Netaji Subhas University,
Jharkhand India.

ABSTRACT

Water is essential for everything we do, including drinking, washing, cleaning, and other activities. Without water, life is unimaginable. We need to understand whether the resources we are utilising are appropriate and sufficient for us in order to thrive on the planet. With this concept, we attempted to concentrate on a study that could inform us of the water quality we use on a daily basis. We conducted a number of experiments to determine the chemical and microbiological status of the water in order to concentrate on the study.Through chemical and microbiological research, we were able to identify in this study which places and water samples were deemed safe for human consumption.

KEYWORDS: Water, Chemical, Microbial.

INTRODUCTION

In terms of water resources, India has a network of resources like rivers and snow, which is a form of blessing for the nation and can therefore meet the needs (Bhawan, 2005). Due to their heavy reliance on rivers, the Indian population places a high value on water. Water resources are used for a variety of purposes, including drinking, irrigation, aquaculture, and power generation. Water resource management is realising the necessity of ongoing hydrological studies on Indian waterways due to the extensive utilisation of fresh water resources.The presence of various disease-causing bacteria in drinking water and recreational water is discussed in a number of studies, including one from the All India Institute of Medical Sciences (AIIMS), New Delhi. The usage of this water results in a number of serious illnesses. According to reports, human activity is the primary cause of pollution in the Indian River system (Goer et al; 1995). Studies of physical, chemical, and microbiological features

are crucial to understanding the relevance of water as a significant ecological element.Surface water microbiological characteristic are significantly impacted by sewage plant discharges and runoff from unincorporated areas. To evaluate the surface waters microbiological quality faecal coliforms (FC), the most prevalent bacterial indicator of faecal contamination, are used as indicator organisms in most cases. These organisms are frequently discovered in water that has been tainted by faeces from both humans and animals. Total coliforms (TC) are made up of both other bacterial groups and bacterial species with faecal origin (e.g. bacteria commonly occurring in soil).Coliforms are analysed to determine the general hygienic condition of the water and any potential risk of infectious diseases from it. High FC and TC counts in water are typically exhibited as diarrhoea, sometimes accompanied by fever and other secondary problems. Children and adults frequently bathe in streams and rivers in the neighbourhood, as is the case with swimming in rivers. The fact that water-borne diseases often have low infectious doses is widely acknowledged. Additionally, there is a great likelihood that you will consume a dose that will make you sick from a bacterium. Water makes up 75% of the human body, which is why it is regarded as essential to life.One of the most vital elements on earth is water. One of the main components that support life on earth is water. As is obvious, water plays a crucial role in our diet by assisting the body's many metabolic processes and regulating our body temperature. Because of its similar density to cell protoplasm, water is special. Water helps people lose weight since it has no calories.

Water is regarded as the essential element that most directly affects the quality of our lives because it is the universal solvent. Without water, life is unimaginable. The same way that water circulates throughout the human body, it likewise does so on land, carrying away waste while transporting, dissolving, and replenishing nutrients and organic matter. The body further regulates the actions of fluids, tissues, cells, lymph, blood, and glandular secretions. Water serves as a vector for diseases brought on by bacteria, viruses, protozoa, and worms.In order to be regarded as potable, water must be pathogen-free. Additionally, it shouldn't contain any other toxic substances, such as pesticides, insecticides, or herbicides, synthetic fertilisers, or heavy metal ions. It shouldn't taste or have an offensive odour.

The infections that are spread by contaminated water are known as waterborne diseases. Over 2 million people per year pass away from the diseases cholera, typhoid, and dysentery, which are transmitted by contaminated water and a shortage of water for hygiene (Mishra and Tripathi, 2000).

MATERIALS AND METHODS

Materials

pH meter, Test tubes, pipettes, auto pipettes, conical flask, glass rod, funnel, beaker, petri plates, burette, measuring cylinder, filter papers, MacConkey broth, filter papers,etc. Water samples were taken from the different areas of Jamshedpur, Jharkhand.

Methods

Chemical analysis of water

To identify and measure the chemical constituents and properties of water samples, water chemistry analyses are performed. The goal of the analysis and the intended use of the water will determine the type and sensitivity of the analysis. The analysis findings give information.

Following tests are performed for chemical analysis of different water samples and calculations are done accordance with WHO 2007:

- pH
- Total dissolved solid
- Total suspended solid

Microbial analysis

Worldwide, water-borne infections are a major contributor to illness and fatalities. The protection of the public's health depends on routine microbiological testing of drinking water sources, recreational waters, and environmental waters. The primary goal of this microbiological analysis experiment was to identify various bacteria and fungi (vu et al; 2014).

RESULTS

According to the chemical analysis, the pH of the well and ground water in region 1(Bhilai pahari, Jamshedpur) was found to be acidic (Table1). The ground water in Region 2 (Talsa, Jamshedpur) was also discovered to be acidic (Table 2). When Total Dissolved Solid (TDS) analysis was carried out, it was found that Region 1 displayed the maximum value of 1600 for well water (Table 1). It was noted that the maximum value of 3000 for ground water for Region 2 (Table 2). Total suspended solid (TSS) measurements were made, and it was found that Region 1 displayed the highest value of 2500 for well water (Table 1).It was noted that the maximum value of 1000 for ground water in Region 2 (Table 2). When microbial growth

analysis was conducted, it was found that Region 1 displayed the highest growth of microorganisms in municipal water (Fig.1). It was discovered that well water from Region 2 had the highest rate of microbial growth (Fig.2).

Chemical analysis

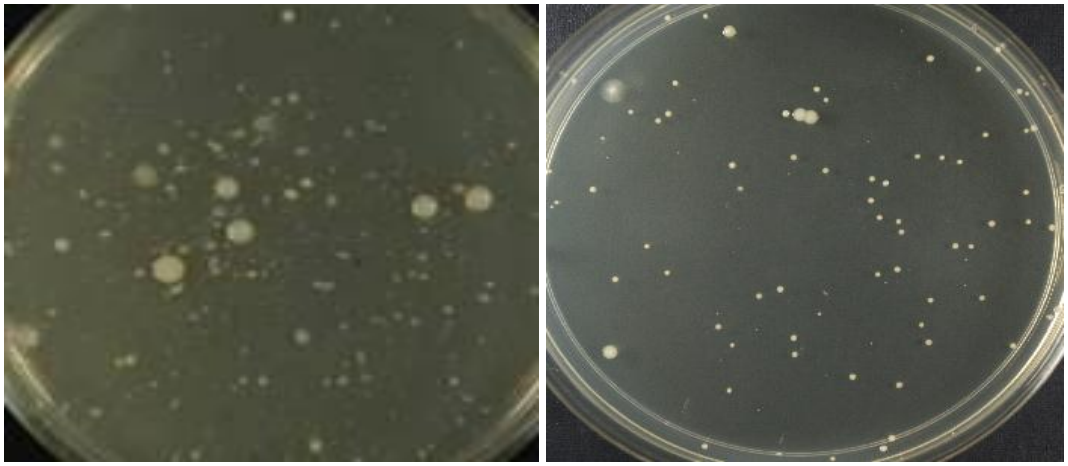
Region 1

Water sample	pH	TDS	TSS	Microbial growth
Well water	6.38	1600	2500	+++
RO water	7.00	400	0.00	nil
Ground water	6.70	800	1500	++++
Municipal water	7.32	400	0.00	Maximium

Region 2

Water sample	pH	TDS	TSS	Microbial growth
Well water	7.00	2500	1000	maximium
RO water	5.72	1000	0.00	Nil
Ground water	6.5	3000	500	++
Municipal water	7.40	0.00	0.00	+++

Figures



(a) **(b)**

Fig. 1: (a) Pictorial representation showing maximum number of microbial colonies in Region 1. (b) Pictorial representation showing maximum number of microbial colonies in Region 2

DISCUSSION

A conclusion that can be drawn from the chemical and microbiological study of several water samples from two distinct regions is that water samples from Region I have perfect pH levels that are equivalent to the studies of (Kulthanan et al, 2013). When compared to water samples from Region II, Region I's water samples may be regarded as safe in terms of the chemicals

they contain. Based on the microbiological study of the two regions' water samples, Region II's agar plates showed the least amount of microbial growth. This can therefore be regarded as potable. Region I water samples did not exhibit any growth on agar plates.However, increase was seen in the water samples from Region II. Therefore, there are no harmful bacteria in Region I. (Ambili and Sebastian, 2015). Overall assessment: Chemical analysis-wise, Region I is secure.

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DIABETES CARE THROUGH PLANT HERBS

Khushboo Jyoti* and Mousumi Ghatak

Netaji Subhas University, Jamshedpur, Jharkhand, India.

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***Corresponding Author**
Khushboo Jyoti
Netaji Subhas University,
Jamshedpur, Jharkhand,
India.

ABSTRACT

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulinaction, or both. A consequence of this is chronic hyperglycemia (that is elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism. Long-termcomplications of diabetes mellitus include retinopathy, nephropathy and neuropathy. The risk of Cardiovascular disease is also increased. Plants are used by people since very early time for food, clothes and even though as a source ofmedicine. Plants derived products have been popular all over the world for the centuries. Some herbs have beta-cells regeneration stimulating power. In addition to maintaining normal bloodsugar level, some herbs are also reported to possess antioxidant activity, cholesterol-loweringaction and restore the liver glycogen level. In this reviewwe attempted to characterize the plants helpful in reducing the diabetes mellitus.

KEYWORDS: Diabetes mellitus, hyperglycemia, cardiovascular disease, plant phytochemicals.

INTRODUCTION

Plants are used by people since very early time for food, clothes and even though as a source of medicine. effect (Malviya et. al, 2010). Plants derived products have been popular all over the world for the centuries. Someherbs have beta-cells regeneration stimulating power. (Chauhan,. et. al, 2010). In addition to maintaining normal bloodsugar level, some herbs are also reported to possess antioxidant activity, cholesterol-lower ingaction and restore the liver glycogen level. Tribal and other people of different countries used different type of plants for the treatment of diabetes (Jarald et. al, 2008). The ethno botanical information reports about 800 plants that may possess anti-diabetic potential and more than 1200 species of plants have been screened for activity on the basis of ethno pharmacology or on random basis. (Jung et.

al, 2006). Herbal anti-diabetic drug mainly belongs to plant, marine algae and fungi to phytogenetically advanced classes of compounds (Warjeet Singh, 2011). Medicinal plants that are the most effective and the most commonly studied in relation to diabetes and its important functions are described in this literature.

1. Swertiacharita

Swertiachirayita is a medicinal plant indigenous to temperate Himalaya. It is known tohave antipyretic, hypoglycemic, antifungal and antibacterial properties. Hexane fraction of S.chirayita (250 mg/kg body wt.) induced significant fall in blood sugar and significant increase inplasma IRI (Chandrasekhar et. al, 1990). Similarly, Petroleum ether, dichloromethane and methanol fraction of Swertiachirata showed hypoglycemic effect on Swiss albino mice (Alamet. al, 2011). Ethanolic extract of Swertia was also found to have beneficial effect on cholesterol and triglyceride level along with anti-diabetic activity (Arya et. al, 2011).

Swertiacharita

2. Gymnemasylvestre

Gymnemasylvestre is a woody, climber, native to India. The leaves of this plant have been used in India for over 2000 years to treat madhumeha, or “honey urine.” Chewing the leaves destroysthe ability to discriminate the “sweet” taste, giving it its common name, gurmar, or “sugardestroyer.” Plant constituents include two resins (one soluble in alcohol), gymnemic acids,saponins, stigmasterol, quercitol, and the amino acid derivatives betaine, choline and trimethylamine (Kapoor LD. 1990). Gymnemasylvestre is a stomachic, diuretic, refrigerant, astringent, and tonic (Kapoor LD. 1990). It has been found to increase urine output and reduce hyperglycemia in both animal and human studies. Gymnema’s antidiabetic activity

appears to bedue to a combination of mechanisms. Two animal studies on beryllium nitrate- and streptozotocin-diabetic rats found Gymnema extracts doubled the number of insulin-secretingbeta cells in the pancreas and returned blood sugars to almost normal (Prakash et al.,1986, Shanmugasundaram et al., 1990). Gymnema increases the activity of enzymes responsible for glucose uptake and utilization (Shanmugasundaram et al., 1983) and inhibits peripheralutilization of glucose by somatotrophin and corticotrophin (Gupta et al., 1964). Plant extracts have also been found to inhibit epinephrine-induced hyperglycemia (Gupta, 1961).

Gymnemasylvestre

3. Eugenia jambolana

In India decoction of kernels of Eugenia jambolana is used as household remedy for diabetes.This also forms a major constituent of many herbal formulations for diabetes. Antihyperglycemic effect of aqueous and alcoholic extract as well as lyophilized powder shows reduction in bloodglucoselevel. This varies with different level of diabetes (Sheela et al., 1992). The extract ofjamun pulp showed the hypoglycemic activity in streptozotocin induced diabetic mice within 30min of administration while the seed of the same fruit required 24 h. The oral administration ofthe extract resulted in increase in serum insulin levels in diabetic rats. Insulin secretion wasfound to be stimulated on incubation of plant extract with isolated Islets of Langerhans fromnormal as well as diabetic animals. These extracts also inhibited insulinase activity from liver and kidney (Acherekar et al.,1991).

Eugenia jambolana

4. Terminalia chebula

The dried ripe fruit of Terminalia chebula (Combretaceae), which is a native plant in India and Southeast Asia, is commonly known as black myroblans in English and Harad in Hindi and has traditionally been used for homeostatic, antioxidant, diuretic, and cardiotonic treatments. T. chebula exhibits in vitro antioxidant and free radical-scavenging activities (Cheng et al., 2003). It is generally assumed that frequent consumption of plant-derived phytochemicals from vegetables, fruit, tea, and herbs may contribute to shift the balance toward an adequate antioxidant status (Halliwell et al., 1995).The attributed anti hyperglycemic effect of these plants is due to their ability to restorethe functions of pancreatic tissues by causing an increase in insulin output or inhibits the intestinal absorption of glucose or to facilitate the metabolites in insulin dependent processes.Hence treatment with herbal drugs has an effect on protecting β-cells and smoothing outfluctuation in glucose levels (Jia et al., 2003, Elder, 2004). In general, there is very little biological knowledge on the specific modes of action in the treatment of diabetes, but most ofthe plants have been found to contain substances like glycosides, alkaloids, terpenoids, flavanoids etc., that are frequently implicated as having antidiabetic effects (Loew et al., 2002).

Terminalia chebula

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Diabetes And Its Connection To Oral Health Issues

Mousmi Ghatak[1], Khushboo Jyoti[2], Dr. Bijendra Rai[3], Dr. Pramod Kumar Singh[4*]

[1,2,4*]Netaji Subhas University, Jamshedpur, Jharkhand, India
[3]Govt. Holkar Science College, Indore, M.P. India

***Corresponding author:** Dr. Pramod Kumar Singh
*Netaji Subhas University, Jamshedpur, Jharkhand, India drsingh2030@gmail.com

Abstract:
Chronic metabolic disease known as diabetes mellitus is a major source of morbidity and mortality in the modern world and is currently on the rise. Patients with diabetes may experience several health consequences, including retinopathy, neuropathy, nephropathy, cardiovascular diseases and oral complications. Diabetes-related oral problems include periodontal disease, dental caries, oral infections, abnormalities of the tongue; salivary glands, delayed wound healing, halitosis, and lichen planus. Oral problems are associated with uncontrolled diabetes, including excessive salivary glucose levels, impaired neutrophil function, neuropathy, and small artery damage. Patients with diabetes have a decline in their quality of life due to oral problems. Even higher blood glucose levels are a result of complications such as periodontal disease, which has a reciprocal association with diabetes mellitus. The purpose of this article is to raise awareness about the oral health of diabetics and to emphasize the significance of keeping good oral hygiene, implementing preventative measures, identifying oral difficulties early on, and managing these patients' oral complications appropriately using a multidisciplinary approach.

Key words: Diabetes Mellitus, Neutrophil, Neuropathy, Periodontal

Introduction:
A chronic, non-communicable metabolic disease called diabetes mellitus is characterized by abnormal insulin secretion, action, or both. The metabolism of fat, protein, and carbohydrates is disrupted when there is insufficient insulin. Diabetes Mellitus develops as a result of both environmental and genetic causes. The end effect of decreased insulin secretion, decreased glucose utilization, or increased gluconeogenesis is hyperglycemia and detrimental alterations in several organs. [1,2]. Diabetes is categorized into the following general categories: Type 1 diabetes, Type 2 diabetes, and certain types of diabetes brought on by other factors such as exocrine pancreatic disease, diabetes brought on by chemicals or drugs, and monogenic diabetic syndrome (d) Diabetes mellitus during pregnancy. [3]. Currently, 422 million people worldwide suffer from diabetes mellitus. There are 1.6 million deaths annually that are directly related to diabetes. [4]. The International Diabetes Federation has estimated that 693 million people between the ages of 18 and 99 would have diabetes by the year 2045, based on data from research conducted around the globe. [5]. As diabetes becomes more common, complications are expected to have a major negative influence on society and the economy. [6–10]. Diabetes can cause severe hypoglycemia or ketoacidosis, which are acute consequences. Retinopathy, neuropathy, cardiovascular disease, and nephropathy are a few examples of chronic disease consequences. [11–14].

One area of the body where chronic hyperglycemia affects people is the mouth cavity. Diabetes mellitus-related oral health complications are brought on by impaired neutrophil function, microangiopathy, neuropathy, decreased collagen production, and decreased collagenase activity. [15]. Over 90% of diabetic patients experienced oral problems, according to a research. [16]. An additional systemic review has found that patients with Diabetes Mellitus have higher rates of oral mucosal disorders than people without the disease: 45–88% of patients with Type 2 diabetes compared to 38.3–45% of non-diabetic subjects, and 44.7% of type 1 diabetics compared to 25% of the non-diabetic population. [17]. Diabetes Mellitus can lead to issues in the oral cavity, including tooth decay, gingivitis, oral candidiasis, altered taste, geographic tongue, fissured tongue, dry mouth, infection predisposition, oral lichen planus, and poor wound healing. [18–23]. One of the oral consequences of Diabetes Mellitus that gets worse because of hyperglycemia is periodontal disease. In addition, there is a reciprocal association between diabetics' blood glucose levels and systemic inflammation brought on by periodontitis. [24]. Periodontal disease incidence and prevalence are impacted by diabetes mellitus. Uncontrolled diabetes is characterized by the formation of deep pockets and loss of attachment, and people with diabetes have a high prevalence of periodontitis, ranging from 34% to 68%. [25, 26]. Uncontrolled diabetes increases the chance of alveolar bone loss eleven times over in healthy individuals. [18]. Xerostomia, or dry mouth, is a condition that has been linked to diabetes. A meta-analysis encompassing 32 studies revealed that 46.09% of individuals with diabetes experienced xerostomia, and another study discovered that diminished salivary flow affected 92.5% of diabetic patients. [27, 28]. Dysphagia, dental caries, mouth discomfort, and dysgeusia are eventually caused by this condition, which tends to reduce the quality of life for diabetics. [28–31]. Patients with diabetes have a higher risk of oral infections and delayed wound healing. [32, 33]. Oral bacterial infections are made easier by an elevated

glucose level in the oral cavity and the immunocompromised state of uncontrolled Diabetes Mellitus. [18,32]. Diabetes mellitus patients may experience delayed wound healing because of damaged tiny blood arteries and compromised immune system response to inflammation and infection. [33–35].

Due to hyposalivation and elevated salivary glucose levels, which encourage the growth of the bacteria that cause tooth caries, diabetic people also experience dental caries. [36–38]. These individuals may experience oral health issues such as taste dysfunction, a condition in which diabetics lose some of their capacity to discriminate flavours. [39–41]. One type of neuropathic orofacial discomfort is Burning Mouth Syndrome. [42]. Patients with diabetes may experience fissured tongue, atrophic glossitis, rhomboid glossitis, or benign migratory glossitis. [23, 43, 44].

Oral Manifestations Disease in Diabetes Mellitus

There are four types of periodontal health: pristine (no attachment or bone loss) periodontal health is characterized by the complete absence of physiological immune surveillance and clinical inflammation on a periodontium with normal support. (b) clinical periodontal health, in which the periodontium's natural support is present and clinical inflammation is absent or at a minimal (d) periodontal disease remission or control in a reduced periodontium; (c) periodontal disease with impaired stability in a periodontium. [45]. A persistent inflammatory disease called periodontitis is brought on by pathogenic biofilm that builds up on teeth [46]. It has been proposed that *Tannerella forsythia, Treponema denticola*, and *Porphyromonas gingivalis* are the main gram-negative bacteria that cause periodontitis. [47, 48]. The inflammatory loss of periodontal bone can be triggered by *P-gingivalis*. [49]. These bacteria's DNA and lipopolysaccharides trigger the production of inflammatory cytokines by triggering the pathways of nuclear factor κβ (NFκβ) and protein-1. [50 - 51]. Neutrophils are drawn to cytokines, which increases the generation of reactive oxygen species (ROS). Tissue damage is caused by osteoclast activation caused by AP-1 and NFκβ. [52 – 53]. Certain bacteria species may proliferate in diabetic crevicular fluid due to elevated glucose levels. [54]. It has been observed that diabetic patients with periodontitis have much greater levels of local mediators of inflammation, such as prostaglandin E2, TNFα, and IL-1β, which results in extended osteoclast production and activity. [54–56]. Diabetes-related up regulation of interleukin stimulates osteoclast formation, extending the length of the inflammatory response. [57 – 59]. Additionally, there is an overabundance of RANKL, which stimulates the production and activity of osteoclasts by interacting with receptors on their surface. [60 – 63]. Increased AGE production that interacts with RAGE is present in diabetes mellitus. Thus, more RANKL receptor activator is formed, which further encourages osteoclast generation. [64]. Additionally, AGE-RAGE interaction enhances the production of inflammatory cytokines and activates NFκβ. [65]. Compared to healthy people, diabetic patients' neutrophils release more super-oxides. [65]. Through oxidative stress, increased ROS significantly contributes to the death of periodontal tissue. [64]. In diabetics, TNFα, AGEs, and ROS production cause osteoblast apoptosis. [66]. A caspase-3-dependent pathway enables the death of fibroblasts and epithelial cells caused by periodontal infection in individuals with diabetes mellitus. [67]. Diabetes Mellitus causes enhancement and apoptosis, which impair repair and cause the loss of the epithelium barrier's protective properties. [68- 70]. Uncontrolled Diabetes Mellitus patients are more prone to periodontal disease, also known as gum disease, which encompasses a variety of disorders affecting the gingiva, ligaments, and bones that support teeth. 71 -75]. Dental plaque bacteria cause localized gingival inflammation, which if left untreated leads to chronic periodontitis with gingival, ligament, and bone loss that forms "pockets" in the deeper periodontium. Tooth loss could result from this. [76 – 80]. Hyperglycemia influences the course of periodontal disorders, and periodontitis negatively impacts blood glucose levels as well. This worsens the consequences of diabetes. [24]. Increased cytokines in the saliva and crevicular fluid of periodontal and gingival tissue; oxidative stress accompanied by the production of advanced glycation end products in a hyperglycemic state; and excessive inflammation ultimately lead to the destruction of periodontium. [81]. Diabetes also impairs the development of new bone in the periodontium and raises the expression of RANKL. [82]. Conversely, periodontal disease exacerbates blood glucose management in patients with Type 2 diabetes. Through the release of pro-inflammatory cytokines, it produces systemic inflammation, leading to bacteremia and insulin resistance. [83]. The inflammatory periodontium serves as a persistent reservoir for bacteria, their byproducts, and inflammatory mediators such as TNF α, IL 1, and IL 6 that impact glucose metabolism. [84]. By killing pancreatic β cells, opposing the action of insulin, and changing the intracellular signalling of insulin through NFkβ, the systemic inflammatory cytokines generated as a result of periodontal inflammation also cause insulin resistance. [85]. When comparing diabetic individuals with Type 2 diabetes who underwent dental treatment for periodontal disease to those who did not, improvements in glycemic control were noted. [86]. When compared to diabetic patients who did not receive dental treatment for periodontal disease, patients with Diabetes Mellitus who underwent non-surgical treatment of the periodontium showed improved glycemic control in a meta-analytic study involving nine randomized clinical trials. [87].

Salivary Dysfunction

Xerostomia is the subjective issue of dry mouth, while hyposalivation is the objective decrease in salivary flow. [29]. Systemic disorders such as diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, metabolic disorders such as anaemia, bulimia, dehydration, infections such as HIV/AIDS and HCV, neurological disorders such as Parkinson's disease and depression, and other conditions like sarcoidosis are associated with Xerostomia. [29, 88, 89]. Research has revealed a connection between Xerostomia and Diabetes Mellitus (Type 1 and

Type 2). [28, 30, 31]. Xerostomia may arise in people with uncontrolled diabetes because to problems such as autonomic neuropathy, structural alterations in the salivary glands, and inflammatory changes brought on by hyperglycemia. [15, 90]. The amount and makeup of saliva may decrease as a result of this. [91]. Xerostomia patients experience peeled and cracked lips, glossitis, cervical caries, and dry buccal mucosa. When dysgeusia, dental caries, periodontal disease, mouth discomfort, and dysphagia finally emerge in Xerostomia patients, their quality of life gradually declines. [29].

Infections of the Oral Cavity

Diabetes mellitus patients have weakened immune systems, which makes them more vulnerable to infections of the oral cavity (owing to defence function impairment). [91,92]. In teeth, the bacteria mix with food to generate plaque, which can lead to dental cavities, gingivitis, halitosis, and mouth sores. [32]. When diabetics have an oral infection, *P. gingivalis, Propionibacterium acnes, Actinomyces israelii, Peptostreptococcus prevotii, Fusobacterium nucleatum, Saccharomyces cerevisiae, Streptococcus sanguis, Prevotella intermedia,* and *Streptococcus intermedius* are frequently found bacteria in the oral cavity. Bacterial growth is promoted by the elevated glucose levels in the saliva of diabetes individuals. [18]. Uncontrolled diabetes increases the risk of bacterial infections reoccurring and spreading from the mouth to other parts of the body. Previous research has shown that people with diabetes can get deep neck infections. [93–97].

Poor Wound Healing of the Oral Cavity

Patients with uncontrolled diabetes have poor oral wound healing and related long-term consequences. [33]. Diabetes-related chronic problems are caused by damage to tiny blood vessels. [34]. The food supply to cells that carry out an inflammatory role and protect against infectious pathogens is hampered by an inadequate blood supply. [92]. Healthy tissue replaces dead or damaged tissues when there is inflammation. The body's defence cells are paralyzed by transient blood sugar surges, leaving the body with little defence against infection and inflammatory processes. Hyperglycemia impairs the ability of uncontrolled diabetic patients to repair and regenerate tissue. [33, 35].

Dental Caries

Dental caries is an infectious disease of the teeth caused by bacteria, primarily Streptococci mutans that attaches to the tooth and produces acid from sugar, dematerializing the tooth structure. Dental caries can be caused by a variety of reasons, including fermentable sugar, microbial flora, and environmental variables. [98]. Prior research has shown a connection between diabetes mellitus and the development of dental caries. [28,99]. Dental caries production in Type 1 Diabetes Mellitus has been linked to elevated salivary glucose levels, decreased salivary flow, changes in the biochemical makeup of saliva, a reduction in the salivary buffering effect, poor oral hygiene, a cariogenic diet, and pre-existing dental plaque. [100]. Dental caries is more common in those who consume sugar without any limits than in people whose blood glucose levels are under control. [43]. As people age, dental caries in the cementum of their teeth grow more common, and older patients with Type 2 Diabetes Mellitus have been reported to have caries of the radicular portion of their teeth. [34]. Hyposalivation was cited as a cause of poor oral hygiene in Type 1 diabetic patients in a study comparing their cleanliness to that of a control group. [101]. In 2017, a study found that using sugar-free toothpaste raised salivary pH and decreased salivary glucose levels in people with diabetes mellitus. The study also recommended tight blood glucose management to maintain good oral hygiene.[102]. Patients suffering with Diabetes Mellitus are particularly vulnerable to dental caries because of hyposalivation and elevated salivary glucose levels, which might be a sign of insulin insufficiency. [36]. Saliva's protecting, buffering, and cleaning properties are lost in diabetics. [37]. The basement membrane of the salivary glands alters when the microvasculature is damaged. Therefore, there is an increase in glucose leakage from the duct's cells, which raises the amount of glucose in saliva and the crevicular space. This alteration leads to a decrease in fibroblast activity, which in turn causes an increase in plaque development. Dental plaque changes the glucose in saliva into lactic acid, which lowers the pH of saliva. [103,104]. This low pH promotes the growth of aciduric bacteria, which in turn reduces the growth of oral protective bacteria. The natural environment is shifting in a way that benefits the bacteria that cause dental caries. This lowers pH even further, and the cycle keeps repeating. [37, 38].

Taste Dysfunctions

A person's ability to recognize food taste influences their diet, nutrition, quality of life, and may even contribute to the onset of chronic diseases. [105]. There are at least five different types of taste sensations: umami, bitter, sour, sweet, and salty. [106]. The taste buds and papillae in the oral cavity contain taste receptor cells that detect taste. Signals are sent from taste molecules to taste receptors and then to the brain through the cranial nerve. [107]. Unhealthy eating habits may result from the malfunction of one or more taste receptors, which change how one perceives flavour. [108]. Research has indicated that diabetes mellitus (type 1 and type 2) causes a loss in the ability to distinguish and recognize taste sensations. [39–41]. Diabetics without neuropathy have also been reported to have taste impairment. [109].

Burning Mouth Syndrome

The International Association for the Study of Pain has certified burning mouth syndrome as a neuropathic orofacial pain disorder characterized by oral mucosal burning pain, typically affecting the anterior two thirds of the tongue

without obvious mucosal disease. [42]. The mucosa of the oral cavity is experiencing tingling and burning that has no apparent cause. [110]. In patients with peripheral neuropathy who have type 2 diabetes, this syndrome has been reported in 18.8% of cases. [112]. In individuals with type 2 diabetes, uncontrolled diabetes and diabetic peripheral neuropathy were revealed to be significant predictors of symptoms similar to burning mouth syndrome. [42]. Increased excitability of the trigeminal nerve was observed in diabetic peripheral neuropathy patients compared to healthy individuals in a 2019 study comparing the nociceptive function of the oral cavity in these patients. Peripheral neuropathy in diabetic patients may result in hyperesthesia and pain perception in the mouth cavity. [112]. Long-term burning pain in the mouth makes it difficult for sufferers to maintain good oral hygiene, which exacerbates the condition of diabetic patients' oral health. [43].

Tongue Abnormalities

The tongue is an organ made up of vallate, filiform, and fungiform papillae muscles. It moves food within the mouth cavity with the creation of boluses for swallowing, facilitates speaking, and uses taste buds on the papillae to operate as a taste organ. [113]. Individuals with diabetes mellitus may experience anomalies in their tongues. According to a 2019 study, people with type 2 diabetes have thick yellow fur and a blueish tongue. The study also recommended screening the tongue for the disease in order to identify it early. [114]. A characteristic observed in diabetics is fissured tongue. On the dorsal tongue surface, this condition is characterized by grooves that vary in depth and size. When material gets lodged in these crevices, symptoms show up. [43,115]. Fissured tongue was found to be associated with diabetes mellitus in a study conducted in 2015. [115]. Reduced salivary flow rate and xerostomia can lead to the production of fissured tongue. [116]. The absence of fungiform and filiform papillae on the tongue's dorsal surface causes atrophic glossitis, a disorder that eventually changes the tongue's appearance and texture to become smooth and soft. Rhomboid glossitis is a condition caused by an oral candida infection in people with diabetes mellitus. [44]. An erythematous tongue lesion anterior to the circumvallate papillae is indicative of this glossitis. The rhomboid-shaped lesion, also known as a kissing lesion, is located along the dorsal surface of the tongue along the midline. It is smooth, shiny, and depapillated. [117]. Diabetes Mellitus individuals can also have benign migratory glossitis. [113]. This benign condition is characterized by redness (erythema), atrophy of the filiform papillae, and a border of white, hyperkeratosis that is serpiginous. [23].

Halitosis

One of the early signs of diabetes is halitosis, or foul breath, which is a characteristic ketone scent in diabetics. Sulphide compound odour might also result from periodontal disease. Oxidative stress brought on by elevated blood levels of methyl nitrate and fatty acids results in halitosis. [45]. According to a 2015 study, halitosis affected 23.3% of the study participants who were diabetic. [118].

Oral Lichen Planus and Oral Lichenoid Reaction

A persistent inflammatory skin lesion is called lichen planus. [119]. The lesion is characterized by itchy, flat-topped, polygonal, violaceous plaques and papules that can occur throughout the body, including the oral cavity. The oral cavity lesion manifests as white elevated lines that form a bilateral, symmetrical lace-like pattern. Patients with diabetes have been observed to have oral lichen planus in 120 studies. [46,47]. An oral lichenoid reaction is another mucosa-related alteration that could negatively impact oral hypoglycemic medications given to diabetic patients. [48, 49]. The autoimmune condition known as oral lichen planus causes the basal cells of the oral cavity's epithelium to undergo apoptosis, which is facilitated by cytotoxic T lymphocytes. [121]. Oral lichen planus patients may experience pain and burning in their mouths, which can make it difficult for them to swallow and eat. [48]. Given the potential for malignancy, oral lichen planus must be diagnosed and treated to stop the development of oral squamous cell carcinoma. [49].

Other Oral Complications

Prior research has demonstrated that diabetic individuals had little knowledge of the risks associated with oral health and were unaware of the reciprocal relationship between diabetes mellitus and periodontal disease. [122–126]. Several barriers kept the carers from offering effective treatment in a 2017 study on the knowledge and behaviors of diabetes care providers in dental health care. These included a lack of appropriate referral systems, guidelines or dental health screening tools, and insufficient understanding of the reciprocal relationship between diabetes and oral health. [53]. Nonetheless, prior research has indicated that patients with diabetes who receive information on oral health from healthcare providers and have improved education in this field have a solid understanding of oral health. [126,127]. Patients who have more knowledge about the connection between diabetes and dental health adopt healthier dental habits. [128]. Diabetic neuropathies are a varied set of illnesses that are the most common main consequence of diabetes mellitus. Diabetic neuropathies that resemble diffuse neuropathy include autonomic neuropathy, mononeuropathy, radiculopathy, and distal symmetric polyneuropathy, which is the most prevalent kind of diabetic peripheral neuropathy. [129,130]. DSPN is the most common type of diabetic neuropathy, making for to 75% of the complications. [131,132]. A number of variables, such as age, the length of diabetes, and diabetic retinopathy, may raise the chance of developing diabetic peripheral neuropathy. [33]. Diabetic neuropathy can affect about 50% of people with diabetes. [34]. Potential pathophysiological factors of diabetic neuropathy include oxidative stress, inflammation, damage to the

vasa nervorum, the small blood arteries that supply the nerves, neuronal injury, and damage resulting from metabolic disturbances. [129 –137]. Neuropathic pain, which can be searing, shooting, tingling, or lancinating in character, and paresthesia that gets worse at night are symptoms of diabetic peripheral neuropathy. When exposed to certain stimuli, including shoes and bed linens, there could be an increased reaction to pain. Such pain can impair one's quality of life, cause disabilities, and interfere with day-to-day functioning. [38, 138 -140]. Patients with diabetes are frequently diagnosed with cardiovascular problems such as peripheral artery disease and cardiac myopathy later in the course of their illness. [141]. Patients with Type 2 diabetes who have both obstructive and nonobstructive coronary stenosis have shown signs of advanced atherosclerotic alterations in their coronary arteries. [142,143]. Acute coronary syndrome and the loss of myocardial muscle regeneration function are further complications. [143]. Vasoactive amines change the response, which has a negative impact on the heart. [142–144]. Arrhythmias in the ventricle and atria are brought on by a disruption in the genesis and propagation of action potentials in cardiac muscle, which results in automaticity and re-entry mechanisms. The high rate of congestive heart failure associated with diabetes mellitus is caused by pump failure brought on by anomalies in the heart muscle brought on by inflammation and cardiac fibrosis. [144,145]. Changes in diet and lifestyle can help prevent or postpone cardiovascular problems in people with Type 2 Diabetes Mellitus. [146]. Diabetic Retinopathy is a consequence of Diabetes Mellitus that carries a risk of blindness. [147]. Diabetic Retinopathy can occur as a result of prolonged diabetes, high blood pressure, and inadequate blood glucose regulation. [148]. Diabetic retinopathy is largely caused by the generation of free radicals, advanced glycation end products (AGE), and inflammation brought on by hyperglycemia. [149]. There are two forms of diabetic retinopathy: proliferative diabetic retinopathy, which poses a threat to vision, and non-proliferative diabetic retinopathy. [147]. The causes of visual loss in Diabetic Retinopathy include complications from Proliferative Diabetic Retinopathy such as tractional retinal detachment, vitreous haemorrhage, neovascular glaucoma, and diabetic maculopathy. [150]. In diabetic patients, vascular leakage due to microangiopathy results in macular edoema and capillary blockage, which causes retinal ischemia and an increase in vascular endothelial growth factor. Thus, these alterations lead to neovascularization and proliferative diabetic retinopathy. [151,152]. Strict glycemic management in diabetic individuals can stall the eventual progression of non-proliferative diabetic retinopathy into proliferative diabetic retinopathy. [153].

Conclusion

In the modern world, diabetes mellitus has become a serious epidemic. Oral health issues are among the consequences caused by this metabolic condition. A diabetic's quality of life is likely to be negatively impacted by oral problems. These oral difficulties would cause the person to experience difficulty speaking, chewing, swallowing, and unpleasant mouth sensations. They also have an increased risk of oral infections due to taste anomalies, which make them, consume more sugar and salt and worsen their glycemic control, ultimately harming their dental health. Hyperglycemia in diabetic individuals is associated with a number of oral problems, primarily when there is inadequate control of blood glucose levels. Simultaneously, issues like as periodontitis because blood glucose levels to rise and other health difficulties to worsen. When the periodontium is free of inflammation, an individual can function normally without experiencing any negative effects from a former illness, either physically or mentally. This state is known as periodontal health. Diabetes Mellitus compromises periodontal health, meaning that diabetics with periodontitis experience worsening and persistent periodontal inflammation. The reciprocal association between Diabetes Mellitus and Periodontitis stems from the discharge of pro-inflammatory cytokines such as TNF α and interleukins, which exacerbate periodontal disease and induce insulin resistance. Through the death of pancreatic β cells, bacterial endotoxins from contaminated periodontium and systemic inflammatory cytokines lead to insulin resistance and hyperglycemia. It is important to raise awareness of these oral health issues since good dental hygiene can lessen their frequency and severity. Taking care of these oral cavity issues in diabetic individuals requires a multidisciplinary team that includes doctors and dentists. The blood glucose level and general health of the oral cavity can be maintained under control with routine dental and medical visits via prevention, early detection, and appropriate care.

Recommendation

The human body is severely affected by the relationship between Diabetes Mellitus and oral cavity issues. It is necessary to raise awareness of the oral health issues that diabetics face. Patients with diabetes should get education regarding the heightened dangers to their oral health, as well as tips for maintaining good oral hygiene and scheduling frequent dental checkups. Every time a patient with diabetes visits a dentist or physician, a periodontal screening should be performed. Strategies for managing and assessing diabetic patients at risk should be implemented in order to prevent the emergence of such oral problems. To effectively treat these diabetic patients' oral health, dentists must collaborate with medical professionals in related professions. The Diabetic Association can provide handbooks that explain diabetic care difficulties and assist dentists in identifying better indications and symptoms that call for a referral or annual screening. This will therefore enable a proactive approach to diabetic care that goes beyond the purview of their field. Additionally, pamphlets on maintaining dental hygiene for those with diabetes might be made available to the general public. Doctors and dentists should never stop emphasizing to their diabetic patients how crucial glycemic control is to preserving their quality of life.

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Original article

Therapeutic efficacy of water extract of Oyster Mushroom in streptozotocin induced diabetic Wistar rats

Mousumi Ghatak[1], Dhananjay Yadav[2], Sung Hae Kim[3], Pramod Kumar Singh[1]

[1]Department of Zoology, Netaji Subhas University, Jamshedpur, Jharkhand, India; [2]Department of Life science, Yeungnam University, Korea; [3]Department of Molecular Biosciences, The University of Kansas, Lawrence, KS 66045, USA

Abstract. *Back ground and aim:* Currently, there are a lot of allopathic medications on the market that are very effective at controlling diabetes, but they eventually cause side effects. Plant derived products have proven to be effective and safe in the treatment of diabetes mellitus due to the presence of active bioactive compounds which have attracted scientists into the look insight of the natural products. Oyster mushroom is a low – calorie, fat free, fibre-rich food high in various vitamins and minerals such as copper, niacin and phosphorus. Hence, the present study was evaluated the potential effect of anti-hyperglycemic, anti-hyperlipidemic and anti-oxidative properties of oyster mushroom extract in streptozotocin induced diabetes. *Methods:* 32 rats (N=32) were given a standard diet and divided into four groups namely Group 1: normal control (NC), n=8, Group 2: Diabetic control (DC), n=8, Group 3: A dose of 200 mg/kg BW of oyster mushroom aqueous extract treatment for diabetic rats, n=8, Group 4: Glibenclamide treatment for diabetic rats or rats treated with allopathic drug, n=8. All the biochemical estimations were done at two different intervals, one after the induction of diabetes and second after completion of (21-day) therapy. *Result:* The present study was investigated for the quantitative analysis of phytochemicals, antioxidants, α-amylase inhibitory activity and antidiabetic properties of aqueous extract of oyster mushroom. Quantitative analysis of aqueous extract shows phenolics, flavonoids, tannins, alkaloids and saponins as bioactive compounds. Furthermore, using DPPH radical scavenging activity, hydrogen peroxide scavenging activity, total antioxidant capacity, and anti-haemolytic activity were found to be 54.41±1.18, 11.87±1.21, 29.23±3.12, and 14.42±4.89 (activity measured in % inhibition). In the next phase of our study, we evaluated the α-amylase inhibitory activity of the extract in a dose dependent manner and found the inhibition of (89.96±4.6 % at 1000 μg/ml). Finally, oyster mushroom extract was administered to diabetic rats (200 mg/kg) for 21 days to examine its anti-hyperglycemic, anti-hyperlipidemic and anti-oxidative properties. *Conclusion:* A significant reduction in triglyceride, total cholesterol, and low-density lipoprotein-cholesterol (LDL-C) was demonstrated by the extract. Furthermore, oyster mushroom aqueous extract improved high density lipoprotein- cholesterol (HDL-C) levels as well antioxidant enzymes.

Key words: Streptozotocin, Wistar rats, type -2 diabetes, Oyster Mushroom

Introduction

Lack of insulin and insulin dysfunction cause diabetes, a life-threatening disease characterized by elevated blood glucose levels (1). The treatment of diabetes mellitus, especially type-2 diabetes, is necessary to control blood sugar levels.; if not treated caused major complications like cardiovascular diseases, nephropathy and neuropathy which is the major threat of mortality and serious morbidity in the developing country (2, 3). Many allopathic drugs are available in the market which is excellently working

in the control of diabetes but ends with side effects after prolonged use (4-6). However, plant derived products have proven to be effective and safe in the treatment of diabetes mellitus due to presence of active bioactive compounds which have attracted scientists into the look insight of the natural products (7-10). The fungi are among the most popular natural resources due to their low calories content but their high content of proteins, carbohydrates, fibres, vitamins and minerals, as well as their essential bioactive compounds that are reported to aid in the prevention of diabetes mellitus and many more diseases (11-13). Mishra and Singh, 2010 (14), studied how an aged Swiss albino rat's lipid profile, lipid peroxidation, and liver function were affected by dried mushrooms and mushroom extract. Dried mushrooms and their extract can increase antioxidant status throughout aging and reduce the emergence of age-related illnesses caused by free radicals (14). A similar study in which rats fed 10% dried mushroom, 300 mg mushroom extract, and 300 and 600 mg L-carnitine had lower total lipids, including triglycerides, total cholesterol, low-density lipoprotein, and very low-density lipoprotein, as well as liver enzymes and lipid peroxidation. Furthermore, 10% dry mushroom and 300 mg L-carnitine supplementation improved rat liver tissues (15). The consumption of oyster mushrooms decreases total cholesterol, total triglycerides, and low-density lipoprotein, while increasing high-density lipoprotein levels (16). According to research by Alam et al., 2009 (17), feeding hypercholesterolemic rats 5% powdered oyster mushrooms *(Pleurotus ostreatus, P. sajor-caju, and P. florida)* decreased the plasma levels of triglycerides by 45%, 24%, and 14%, and total cholesterol by 37%, 21%, and 16%, respectively. Besides containing medicinal importance oyster mushrooms also have macronutrients, micronutrients (vitamins) and non-nutrients such as phenolics which is associated with anti-oxidants properties (18). Oyster mushroom are a low –calorie, fat free, fiber-rich food high in various vitamins and minerals such as copper, niacin and phosphorus (19-20). Hence, the present study was evaluated the potential effect of anti-hyperglycemic, anti-hyperlipidemic and anti-oxidative properties of oyster mushroom extract in streptozotocin induced diabetes.

Material and Methods

Experimental design

32 rats (N=32) were given a standard diet and divided into four groups namely Group 1: normal control (NC), n=8, Group 2: Diabetic control (DC), n=8, Group 3: Aqueous extract treatment for diabetic rats, n= 8, Group 4: Glibenaclamide treatment for diabetic rats or rats treated with allopathic drug, n=8. All the biochemical estimations were done at two different intervals, one after the induction of diabetes and second after completion of (21-day) therapy.

Preparation of water extract of mushroom and other analysis

Using the method described by Sze Han et al. 2015 (21). We prepared aqueous extracts of oyster mushrooms. A dose of 200 mg/kg BW of juice was administered daily to mice (22). The powder form of Oyster mushroom was obtained from the OMCAR India, Gwalior M.P. The Folin-Ciocalteu colorimetric method of Mallick and Singh 1980 (23) was used to estimate the total phenolic content (TPC) of the sample. Tannins were measured as tannic acid equivalents (24). Alkaloids and flavonoids were detected by methods described by Harborne, 1973 (25). Determinations of Saponins were performed by the methods of Brunner (1984) (26). α-amylase inhibitory activity was measured using the methods of Miller, 1959 (27). Various antioxidant parameters including scavenging of free-radicals DPPH, hydroxyl radicals; hydrogen peroxide scavenging, total antioxidant capacity; anti-lipid per-oxidation and anti-haemolytic activity was done according to the standard procedure of Shabbir et al., 2013 (28).

Induction of diabetes

To induce diabetes in overnight fasted rats (Brosky and Logothelopoulos, 1969 (29), a freshly prepared STZ solution in 0.1M citrate buffer, pH 4.5 was intraperitoneally injected. An ACCU-CHEK sensor glucometer was used at 72 hours following streptozotocin injection to confirm hyperglycemia or increased blood glucose level. For various biochemical analyses,

blood samples from experimental rats of each group were collected from bleeds of the retro-orbital plexus of the rats in each group.

Blood collection

All the biochemical estimations were done at two different intervals, one after the induction of diabetes i.e. in pre-treated animals (0-day estimation) and second after completion of 21 days of therapy i.e. in post treated animals (21 days estimation).

Biochemical analysis

Various lipid profiles were studied, such as the total cholesterol (TC) measured by Stockbridge et al., 1989 (30), the triglyceride (TG) concentration by Fossati and Prencipe (1982) (31), HDL-cholesterol calculated by Lopes-Virella et al., (1977) (32), and low density lipoprotein (LDL) and very low density lipoprotein (VLDL) dosed by Freidewald's Formula. A variety of kidney function tests were performed, such as serum creatinine calculated by Bowers and Wong (1980) (33), serum urea calculated by Fawcett and Scott (1960) (34) and serum uric acid calculated by Fossati et al., (1980) (35). The serum glutamic-pyruvic transaminase (SGPT) as well as serum glutamic-oxaloacetic transaminase (SGOT) were calculated by Reitman and Frankel (1957) (36), and the serum bilirubin was calculated by Fuehr (1964) (37). All these parameters were estimated by using kits manufactured by Crest Biosystems, Pvt. Ltd. India.

Oxidative stress markers in blood

Oxidative stress enzymes like GSH were calculated using Ellman 1959 (38), superoxide dismutase (SOD) was calculated using Winterbourn, 1975 (39). Thiobarbituric acid reacting substance (TBARS) was calculating using Ohkawa et al., 1979 (40), Catalase was calculated using Sinha 1972 (41), and protein concentration was estimated by the method of Lowry et al; 1951 (42).

Statistical analysis

An ANOVA with Tukey's post-hoc analysis of variance was performed using Sigma Stat 3.5. Statistical significance was determined at $p<0.05$ among eight animals in each group, with results expressed as mean ± SEM. A value of was considered significant and results are expressed as mean for eight animals in each group.

Results

Using streptozotocin inducement of diabetes, this study evaluated oyster mushroom extract for its anti-hyperglycemic, anti-hyperlipidemic, and antioxidative properties. Detailed results are presented below.

Screening of phytochemicals

The aqueous extract of mushroom was tested for the evaluation of phytochemicals showed (Table 1), in terms of phenols, tannins, flavonoids, saponins and alkaloids using Gallic acid standard. The major constituents found were phenols and flavonoids whereas tannins, glycosides and saponins were reported less in amount. All these phytochemicals are reported as potent antioxidant activity (43).

Antioxidant property of aqueous extract of Oyster mushroom

The antioxidant properties of aqueous extract of oyster mushroom are shown in the Table 2.

Table 1. Phytochemical constituents of Oyster mushroom.

	Phenolics (mg/gm)	Flavonoids (mg/gm)	Tannins (mg/gm)	Alkaloids (mg/gm)	Saponins (mg/gm)
Aqueous extract of oyster mushroom	0.84±0.03	0.69±0.01	0.29±0.04	0.04±0.03	0.002±0.02

All values are the average of three determinations. (Means± standard deviation SD). Significant at ($P \leq 0.05$).

Table 2. Antioxidant activities of Oyster mushroom.

S.No	DPPH (%Inhibition)	H2O2 (% Inhibition)	Total AO (%Inhibition n)	Egg Albumin (%Inhibition)	Goat Liver (%Inhibition)	Antihemolytic activity (% Inhibition)
Aqueous extract of oyster mushroom	54.41±1.18	11.87±1.21	29.23±3.12	32.58±2.54	46.78±0.08	14.42±4.89

All values are the average of three determinations. (Means± standard deviation SD) Significant at ($P \leq 0.05$).

Table 3. α-amylase inhibitory activity.

Sample concentration (µg/ml)	α-amylase inhibition activity (%)
100 µl	13.85±0.05
200 µl	18.12±0.03
300 µl	27.35±0.03
400 µl	33.87±0.02
500 µl	46.74±0.05
600 µl	58.69±0.02
700 µl	68.22±0.53
800 µl	72.63±0.04
900 µl	87.23±0.04
1000 µl	89.96±4.6

Table 4. Effect of 21 days therapy on fasting blood glucose levels.

Treatment Serum	Glucose Level	
	0-Day (mg/dl)	21-Day (mg/dl)
Normal control	86.64±1.76	79.32±0.03**
Diabetic control	475.75±6.54	465 ±3.28
Diabetic+Glibenclamide (0.5 mg)	446.23±3.58	144.75±1.95**
Diabetic+Mushroom extract (200 mg/kg) body weight	463.88±0.02	393.46±0.89**

Data was analysed by paired t-test. Value is statistically significant at $P<0.05$(*)

On analysing the different antioxidant properties of extract, it shows activity ranging from (14.42±4.89 to 54.41±1.18). The free radical activity was calculated using the DPPH hydroxyl radical-scavenging activity and found to be (54.41±1.18). The total antioxidant capacity (TAC) was found to be (29.23±3.12). The lipid per oxidation assay was analysed using the egg albumin and goat liver and found the inhibition of 32.58±2.54 and 46.78±0.08 respectively. Haemolytic activity was performed using the goat erythrocytes and found the inhibition of (14.42±4.89) (Table 2).

Evaluation of α-amylase inhibitory activity

α-amylase is an enzyme which helps in the breakdown of starch into free glucose, and absorbed by the small intestine. Nowadays, the inhibition of this enzyme is one of the most important approaches to treating type 2 diabetes mellitus. So, the food grains are tested for the α-amylase inhibitory activity and identified as staple food for the treatment of diabetes. In this research we also attempted to characterize the α-amylase inhibitory activity of the extract in a dose dependent manner and found the inhibition of (89.96±4.6 % at 1000 µg/ml) (Table 3).

Evaluation of anti-diabetic potential of aqueous extract of mushroom

On analysing the results, the streptozotocin induced diabetic rats exhibited significantly higher fasting blood glucose levels (475.75±6.54 mg/dl) as compared to those of normal rats (86.64±1.76 mg/dl) (Table 4). After 21- day therapy of mushroom extract, in diabetic Wistar rats, fasting blood glucose levels decreased by about 15.18% compared to pretreatment levels. The fasting blood glucose levels in diabetic rats treated with glibenclamide showed reduction of 67.56 % compared to pretreatment values.

Effect of water extract of mushroom on plasma insulin levels

Plasma insulin level was checked by the methods proposed by Baskaran et al., 1990 (44) (Table 5).

The plasma insulin levels increased from mean pretreatment value of 0.33±0.03 to 0.35±0.01 µg/L. The plasma insulin levels of glibenclamide treated group increased from 0.33±0.03 to 2.14±0.04 µg/L. The increase in plasma insulin level of glibenclamide treated groups was significant at (P<0.05).

Evaluation of anti-hyperlipidemic potential of mushroom extract

Compared with the normal control rats, diabetic rats showed significantly higher levels of total cholesterol (TC), TG, LDL, and VLDL, while HDL levels were significantly reduced (Table 6). The administration of aqueous extract of mushroom showed significantly reduction of TC, TG, LDL and VLDL as 20.84%, 29.81%, 35.54%, and 29.81% and increased of 29.05 % of HDL was obtained compared with diabetic control group (Table 6).

Effect of aqueous extract of mushroom on biomarkers of toxicity

On evaluating the results of kidney biomarkers showed the increased level of serum urea, uric acid and creatinine, in diabetic control groups of rats induced by STZ as compared with control group (Table 7).

The levels of urea, uric acid and creatinine were significantly increased by 60.65%, 69.87 % and 27.90% respectively. Interestingly, diabetic rats treated with mushroom extract for 21 days showed significant (P<0.05) reductions in urea, uric acid, and creatinine levels, respectively, by 5.23%, 33.99%, and 14.45% (Table 7).

Table 5. Effect of 21 days therapy on plasma insulin levels.

Group	Mean (µg/L)
Normal control	2.86±0.08
Diabetic control	0.33±0.03
Diabetic+Glibenclamide (0.5 mg)	2.14±0.04**
Diabetic+Mushroom extract (200 mg/kg) body weight	0.35±0.01

Table 6. Effect of 21 days therapy on Lipid Profile.

Group	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
Normal control	50.15±3.58	34.10±0.4	23.93±1.1	19.4±0.05	6.82±0.02
Diabetic control	79.35±4.8	98.48±2.1	13.77±1.3	45.89±0.38	19.69±0.06
Diabetic+Glibenclamide (0.5 mg)	46.60±3.8**	59.79±3.2**	26.81±1.1**	7.84±0.64**	11.95±0.81**
Diabetic+Mushroom extract (200 mg/kg) body weight	62.81±1.2**	69.12±2.9**	19.41±1.4**	29.58±0.88**	13.82±0.67**

Data was analysed by one way ANOVA. Value is statically significant at P<0.05(*).

Table 7. Effect of 21 days therapy on Liver Profile.

Group	UREA (mg/dl)	URIC ACID (mg/dl)	CREATININE (mg/dl)
Normal control	34.46±0.08	2.39±0.03**	0.43±0.05*
Diabetic control	55.36±1.43	4.06±0.05*	0.55±0.04**
Diabetic+Glibenclamide (0.5 mg)	51.45±0.09	3.13±0.06	0.41±0.03***
Diabetic+Mushroom extract (200 mg/kg) body weight	52.7±2.38	2.68±0.02***	0.47±0.03***

Data was analysed by one way ANOVA. Value is statically significant at P<0.05(*).

Table 8. Effect of 21 days therapy on Antioxidant enzymes:

Group	GSH (mg/ml)	SOD (µm/min./mg protein)	CATALASE (µm/min./mg protein)	TBARS (n moles of MDA/ml of blood)
Normal control	3.88±0.03	73.26±5.2	4.56±0.04	387.56±8.65
Diabetic control	2.69±0.02	33.34±0.08	3.84±0.03	576.22±11.21
Diabetic+Glibenclamide (0.5 mg)	3.65±0.04**	55.87±0.05**	4.15±0.02**	464.76±7.87**
Diabetic+Mushroom extract (200 mg/kg) body weight	3.48±0.01**	50.65±0.06**	4.08±0.05**	387.55±9.25**

Data was analysed by one way ANOVA. Value is statistically significant at P<0.05(*).

Evaluation of anti-oxidant potential of Oyster mushroom aqueous extract

In normal control and diabetes control rats, oxidative stress markers such as GSH, SOD, Catalase, and TBARS were evaluated. Rats induced with STZ had decreased GSH, SOD, Catalase levels while TBARS levels were higher (Table 8). GSH, SOD, and Catalase levels increased significantly in diabetic rats after 21 days of treating aqueous extract and glibenclamide, while TBARS levels decreased significantly of 32.74%.

Discussion

The present study reveals that water extract of mushroom has many important phytochemicals such as phenolics, flavonoids, saponins and alkaloids which are reported as antidiabetic and antioxidant properties. In this study, administration of aqueous extract of oyster mushroom (200 mg/kg body weight) significantly decreases the elevated blood glucose level; compared to glibenclamide antidiabetic drugs, HDL-C was increased with TC, TG, LDL-C, and VLDL-C. Next, we evaluated the protective effect of mushroom extract against hepatic and renal damage caused by STZ and found the level of hepatic and renal markers near normal levels as compared to treatment with glibenclamide. The study results are in positive correlation with the findings of Prabu and Kumuthakalavalli, 2017 (45) that they found the inhibition of α-amylase with 94.93% reported by administrating the methanolic extract of (200 mg/kg bw) oyster mushroom *pleurotus florida*.

In diabetes, hyperglycemia persists, contributing to the production of free radicals, particularly reactive oxygen species (ROS), which are critical to the damage of the pancreas and insulin loss (46). There was a decrease in antioxidant enzyme expression (approx. half of the original value) in diabetes rats followed by an increase in TBARS (approx. twice the original value). Administration of aqueous extract in the diabetic rats, enhances the value of SOD, Catalase, GSH and reduces the levels of TBARS was recorded after the treatment of 21-day therapy. Similarly, Karim et al. 2020 (47), reported that methanol extract decreased blood sugar levels by 9.8% on the 30th day compared to day 0 and 48.71% (in 30-day) in diabetic mice (treated extract) compared with the respective diabetic control animal while ethyl acetate extract reduced blood sugar by 14.56% on 30th day compared with normal control group and a reduction of 50.85% (30-day) was observed in diabetic rats compared with respective diabetic control group (47). Alternatively, the STZ induces diabetes by increasing plasma cholesterol, triglycerides, LDL-C and lowering HDL levels (46). As a result of oral administration of mushroom extract, diabetic rats demonstrated significant decreases in TC, TG, and LDL-C levels and an increase in HDL-C levels.

An antioxidant is a natural substance which acts against the reactive species generated during the oxidation reactions in the human body. Antioxidant acts through the several mechanisms such as transfer of hydrogen atom, transfer of electrons and the ability to chelate the transition metals (48-49). Free radicals are generated during the metabolism of aerobic cells in the body which produces numerous oxidants which

are responsible for the various diseases (50). These oxidants are involved in the destruction of β-cell function and develop a type 2 diabetes (9). Vishwakarma et al., 2017 (51), studied the four species of oyster mushroom (*Pleurotus cystidiosus, Pleurotus flabellatus, Pleurotus florida, Pleurotus ostreatus*) and evaluated their antioxidant property such as free radical scavenging activity, β-carotene-linoleic acid assay and hydrogen peroxide reducing power activity. All the species have good property of antioxidant activity with the increasing concentration of extract. Our results are in agreement with the findings of Vishwakarma et al., (2017); that on analysing the aqueous extract of oyster mushroom it shows considerable amount of phytochemicals such as phenolics, flavonoids, saponins and alkaloids which are considered as natural antioxidants reported in literature (52). Plasma insulin levels were measured in the present study. Compared to normal control rats, STZ-induced diabetic rats showed a significant decline in plasma insulin levels. Treatment of aqueous extract at 200 mg/kg body weight does not increase the levels of plasma insulin as compared with the allopathic drugs glibenclamide (52), found that metformin at a dose of 150 mg/kg could not make a significant difference in plasma insulin levels in diabetic rats, however, 800 mg/kg of petroleum ether extract of Reishi mushroom increased plasma insulin levels by 78.34% so, in future, administration of higher doses of aqueous extract should be checked. The main approach for treating the type 2 diabetes is to control the blood glucose level. This can be achieved by decreasing the breakdown of glucose through the inhibition of enzyme found in small intestine of the human called α-amylase and α-glucosidase (53-54). These enzymes breakdown the oligosaccharides; disaccharides into monosaccharides and resealed glucose is utilized by the body (55). To evaluate the inhibitory activity against the α-amylase enzyme the aqueous extract of oyster mushroom was tested. In this study we found a dose dependent inhibition of α-amylase with 89.96 % inhibition.

Conclusion

Mushrooms are rich sources of nutrients, fibres and proteins with low amount of lipid and calorific value which are used by human beings since time immemorial. From the above discussion, Oyster mushroom can be useful in treating the diabetes mellitus and a better option for new therapeutic agents against harmful allopathic drugs. Phytochemicals like flavonoids, saponins, phenolics and alkaloids found in this mushroom reduce free radicals generated in the body as well as oxidative stress. The oral administration of aqueous extract of mushroom produces significant hypoglycemic, antidyslipidemic and antioxidant enzymes which lower the glucose level and total cholesterol level in the experimental animal. However, more critical investigations are required to explore the therapeutic potentials of mushroom with effects on insulin level.

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Conflicts of Interest: None.

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Correspondence:
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Pramod Kumar Singh
Department of Biotechnology, Netaji Subhas University, Jamshedpur, Jharkhand, India. Pin: 831001
E-mail: pramod.raju21@gmail.com

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Polyphenols and their protective effects including mechanisms of action against Diabetes mellitus

Dr. Mousumi Ghatak[1], Dr. Pramod Kumar Singh[1#]

[1]Assistant Professor Department of Zoology, Netaji Subhas University, Jamshedpur
[1#] Professor, Department of Biotechnology, Netaji Subhas University, Jamshedpur.

Abstract

Diabetes mellitus, particularly type 2 diabetes (T2DM), represents a significant global health challenge characterized by insulin resistance and chronic hyperglycaemia. Recent research highlights the protective effects of dietary polyphenols, naturally occurring compounds found in various plant-based foods, against the development and progression of diabetes. This paper reviews the mechanisms through which polyphenols exert their antidiabetic effects, including the inhibition of amyloid aggregation, modulation of oxidative stress, reduction of inflammation, and enhancement of insulin sensitivity. Evidence from clinical trials and observational studies indicates that polyphenol-rich diets, especially those adhering to the Mediterranean dietary pattern, are inversely associated with T2DM risk. The ability of polyphenols to protect pancreatic β-cells from cytotoxicity and improve metabolic parameters underscores their potential as therapeutic agents in diabetes management. This review aims to consolidate current knowledge on the mechanisms of action of polyphenols and their implications for diabetes prevention and treatment.

Key words : Polyphenol, Type2 diabetes (T2DM), Dietary fibres.

Corresponding author: **drsingh2030@gmail.com**

INTRODUCTION

Dietary polyphenols including phenolic acids, flavonoids, catechins, tannins, lignans,stilbenes, and anthocyanidins are widely found in grains, cereals, pulses, vegetables,spices, fruits, chocolates, and beverages like fruit juices, tea, coffee and wine. In recent years, dietary

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polyphenols have gained significant interest among researchers due to their potential chemopreventive/protective functions in the maintenance of human health and diseases.Natural products have been playing an important role in human health. Plants have been traditionally used to combat diseases in the medical traditions of different societies. Therefore, not surprisingly many modern drugs represent plant-derived substances for treating Type 2 diabetes (T2D) mellitus, with multiple prominent examples, such as acarbose, andrographolide, and galegine, which contributed to the discovery of biguanides (Figure 1). With so many successful records, the advantages of natural products-based drug discovery highlight biodiversity of resources, structural and chemical diversity, drug-likeness and biological friendliness, biocompatibility and biological validation, hints on efficacy and safety from application of traditional medicines, opportunities for use as scaffolds for chemical modifications to optimize potency, multi-targeted mechanism of action for diseases of complex etiology, and available to large-scale production by biotechnological approaches.

Phenolics are the intricate category of bioactive molecules produced by shikimate and acetate pathways that occur naturally. Almost all medicinal and edible plants contain phenolic compounds. Among the richest dietary sources of phenolic and polyphenolic compounds are fruits, spices, seeds, and vegetables. Moreover, certain beverages like tea, coffee, and wine contribute significantly to the daily intake of phenolics (Pérez-Jiménez, Neveu, Vos, & Scalbert, 2010). Due to their structural diversity and possessing therapeutic activities, researchers have focused on phenolic compounds exploring their use as medicinal agents. Compounds with one phenolic ring are generally classified as simple phenols, whereas those with more than one phenolic ring referred to as polyphenols (Figure 4). There are four major groups of phenolic compounds: simple phenols (designated as phenolic acid), lignans, stilbenes, and polyphenols (referred to as flavonoids). Among polyphenols, flavonoids represent the wide-ranging metabolites, which include flavonols, flavones, flavanones, isoflavones, and anthocyanins (Figure 3). Phenolic acids are the aromatic carboxylic acid with hydroxyl derivatives that have only one phenolic ring in their structure and are of two types, for example, hydroxybenzoic acid and hydroxycinnamic acid derivatives (Kondratyuk & Pezzuto, 2004). Caffeic, p-coumaric, ferulic, and sinapic acids are the hydroxycinnamic acid derivatives that are more abundant in

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plant as compared to benzoic acid derivatives such as gallic acid, protocatechuic acid, and p-hydroxybenzoic acid.

MECHANISMS OF DIETARY POLYPHENOLS AS ANT DIABETIC AGENTS

Accumulated evidences from in vivo and in vitro investigations suggest a significant function of dietary polyphenols in the prevention and management of T2D through the insulin dependent approaches, for instance, protection of pancreatic islet β-cell, reduction of β-cell apoptosis, promotion of β-cell proliferation, attenuation of oxidative stress, activation of insulin signaling, and stimulation of pancreas to secrete insulin, as well as the insulin independent approaches including inhibition of glucose absorption, inhibition of digestive enzymes, regulation of intestinal microbiota, modification of inflammation response, and inhibition of the formation of advanced glycation end products (Table 1). Moreover, dietary polyphenols ameliorates diabetic complications, such as vascular dysfunction, nephropathy, retinopathy, neuropathy, cardiomyopathy, coronary diseases, renal failure, and so on.

Flavonoids

Flavonoids and extracts rich in flavonoids from coffee, guava tea, whortleberry, olive oil, propolis, chocolate, and cocoa have been widely studied as possible antidiabetic agents. Quercetin was the most widely investigated flavonoid in the literatures for the in vivo and cellular antidiabetic effects in animal and cell models (Shi et al., 2019), followed by kaempferol (Alkhalidy et al., 2018), luteolin (Sangeetha, 2019), myricetin (Li et al., 2017), and naringenin (Den Hartogh & Tsiani, 2019). Compared with these aglycones, flavonoid O-glycosides shown less antidiabetic potential (Xiao, 2017). However, flavonoid C-glycosides, such as vitexin, isovitexin, swertisin, apigenin 6-C-β-fucopyranoside, and apigenin 6-C-(2″-O-α-rhamnopyranosyl)-β-fucopyranoside, exhibited positive antidiabetic activity in hyperglycemic animals (Xiao et al., 2016). There is an increasing demand for new therapeutic agents that can control this metabolic disorder and at the same time bring less adverse health effects (Lv et al., 2019). In this sense, phenolic compounds are bioactive ingredients that can be considered as potential agents for diabetes management (Fig. 2). For example, flavonoids (including the

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subclasses of flavones, flavonols, flavanones, flavanols, anthocyanidins, isoflavones, and flavanonols) have been reported to maintain the survival and function of pancreatic β-cells through molecular mechanisms that involve the reduction of oxidative stress (by increasing endogenous antioxidant capacity, less ROS accumulation and translocation of pro-inflammatory cytokines in β-cells), increased expression of anti-apoptotic genes (e.g., Bcl-2 protein), and reduced expression of pro-apoptotic genes (e.g., caspase-3 and caspase-8) and DNA damage, protecting them against autophagy, apoptosis, necroptosis and cell damage in hyperglycemic conditions (Ghorbani et al., 2019). Moreover, scientific evidence suggests that phenolic metabolites (derived from flavanol, flavan-3-ols, quercetin, and anthocyanins) and phenolic acids (e.g., ferulic, chlorogenic, and caffeic acids) can reduce ROS levels, inflammation and protein glycation, inhibit key enzymes related to carbohydrate metabolism and T2DM, increase glucose transporter 4 (GLUT 4) expression, and glucose uptake, in addition to activating pathways responsible for insulin signaling and secretion, thereby improving blood glucose levels (Chen, et al., 2019). More details on the mechanisms of action of dietary phenolic compounds will be discussed in the following topics.

Chemical agents that generate oxygen-free radicals like ionizing radiations and activated oxygen cause DNA damage which results in mutations, deletion, and similar lethal genetic effects. Oxidative DNA damage causes the development of various oxidative DNA lesions, which may trigger mutations (Halliwell and Gutteridge, 2015). Because of DNA disruption, base moieties and sugar become more vulnerable to oxidation, resulting in protein crosslinking, base degradation, and single-strand breakage (Zadák et al., 2009). Further, OS exerts deleterious effects on DNA leaformation of DNA lesions, which can result in genomic instability and consequently lead to cell death. The guanine (a base of DNA) is most susceptible to oxidation in cellular OS. In the presence of ROS, the oxidation of guanosine to 8-oxoguanosine (8-oxoG) takes place. The formation of 8-oxoG is the most common lesion in the DNA molecule. When 8-oxoG is inserted during DNA replication, it could generate double-strand breaks, which finally causes damage to DNA molecule (Aguiar et al., 2013).

Antidiabetic effects of dietary polyphenols.

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After ingestion, the phenolic compounds are absorbed in the small intestine (5–10% of the total polyphenols ingested) and metabolized in the liver to methoxy, sulfated and/or glucuronidated metabolites by phase II enzymes prior entering the bloodstream. The chemically more complex phenolic compounds that are not absorbed in the small intestine (about 90–95%) reach the colon, where they are metabolized by the microbiota present in metabolites that are simpler to be absorbed. Colonic fermentation of these compounds also causes significant changes in the gut microbiota, in addition to increasing the production of short-chain fatty acids (SCFAs) that are absorbed by specific receptors present in colonocytes. Once in circulation, metabolites derived from phenolic compounds (by metabolism in the liver or gut microbiota) are distributed to various organs and tissues and can have several antidiabetic effects, including increased insulin secretion, inhibition of digestive enzymes and DPP-IV, decreased oxidative stress, protein glycation, and inflammation, improved insulin resistance, among others.

A randomized controlled trial found that a diet naturally rich in polyphenols improves glucose metabolism in individuals at high risk of diabetes (Bozzetto et al., 2015). A 4-week, double blind, randomized, placebo controlled trial involving 32 T2D patients showed that flavonoid-rich grape seed extracts significantly improved the biomarkers of inflammation, glycemia, and oxidative stress in the events of obese T2D subjects at high risk of cardiovascular (Kar, Laight, Rooprai, Shaw, & Cummings, 2009). A double-masked, randomized controlled trial found that the daily intake of flavanol-containing cocoa might improve the vascular function of medicated T2D patients (Balzer et al., 2008). A randomized, double-blind, placebo-controlled trial with 48 T2D patients revealed that a 12-week daily supplementation of PycnogenolR (125 mg), a French maritime pine bark extract rich in procyanidins and bioflavonoids, could increase diabetes control, reduce cardiovascular disease risk factors, and lower antihypertensive medicine use vs controls (Zibadi, Rohdewald, Park, & Watson, 2008). In a double-blind, 8-week randomized controlled study involving in 80 T2D patients, Brazilian green propolis (226.8 mg/day) rich in polyphenols and flavonoids was found to prevent T2D patients from worsing developments in blood uric acid and estimated glomerular filtration rate (Fukuda et al., 2015). A randomized, double-blind, placebocontrolled trial (34 subjects) showed that the supplementation of acacia

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polyphenol (250 mg/day) might improve glucose homeostasis in nondiabetic subjects with impaired glucose tolerance (Ogawa, Matsumae, Kataoka, Yazaki, & Yamaguchi, 2013). Coffee polyphenols can improve peripheral endothelial function following glucose loading in healthy male adults (Ochiai et al., 2014). Coffees with different contents of chlorogenic acids did not show different degrees of influence on glucose or insulin responses in healthy humans (Rakvaag & Dragsted, 2016). Red wine polyphenols were found to have a beneficial effect on insulin resistance and lipoprotein plasma concentrations in a randomized clinical trial involving 67 men with high cardiovascular risk (Chiva-Blanch et al., 2013). A whortleberry extracts rich in anthocyanins significantly lowered the levels of fasting blood glucose, 2-hr postprandial glucose, and HbA1c in a randomized, double-blind, placebo-controlled clinical trial, consisting of 37 T2D patients (Kianbakht, Abasi, & Dabaghian, 2013).

Isoflavones

Significant evidence from epidemiological investigations has shown that soybean isoflavones intake is linked to a lower risk of diabetes (Konishi et al., 2019). Soy isoflavones perform hypoglycemic effects in Goto–Kakizaki diabetic rats via suppression of carbohydrate digestion and glucose uptake in small intestine (Jin et al., 2018) and delay the process of renal interstitial fibrosis in diabetic nephropathic rats (Liu et al., 2018). Among soy isoflavones, puerarin, the 8-C-glucoside of daidzein, showed best hypoglycemic effects via improving insulin resistance and sensitivity, protecting pancreatic beta-cells, exerting ant inflammation activity, decreasing oxidative stress, and inhibiting Maillard reaction and advanced glycation end products formation (Chen et al., 2018; Chen, Yu, & Shi, 2018).

Moreover, puerarin ameliorates diabetic complications, such as cardiovascular complications, diabetic nephropathy, retinopathy, neuropathy, and so on. Genistein benefits type 2 diabetes via remarkably ameliorating hyperglycemia (Fu et al., 2012; Rockwood et al., 2019), enhancing beta-cell proliferation and reducing apoptosis (Gilbert & Liu, 2013), ameliorating cardiac inflammation and oxidative stress (Gupta et al., 2015), Biochanin A showed hypoglycemic effect on streptozotocindiabetic rats (Harini, Ezhumalai, & Pugalendi, 2012).

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Biochanin A significantly reduced insulin resistance, improved inulin sensitivity and lipid profile, and attenuates neuropathic pain in diabetic rats (Chundi et al., 2016). Formononetin treatment reduces insulin resistance and attenuate hyperglycemia in T2D, which may be due to increasing expression of SIRT1 in pancreatic tissues (Oza & Kulkarni, 2018). Methylated isoflavones look like they exhibit better antidiabetic effect than nonmethyl forms. However, it needs further investigation in animals and human studies.

CATECHINS

Catechins are natural polyphenols present in edible and medicinal plants, especially in tea leaves (Khan & Mukhtar, 2018). Catechins show a very low bioavailability. After consumption of a single cup of tea, plasma concentrations of catechins rinse quickly reaching a maximum after 2 hr, to then gradually decrease to reach the basal levels within 8 hr. Pharmacokinetic studies demonstrated that in human cells p-glycoprotein is responsible for both uptake and excretion of catechins (Vaidyanathan & Walle, 2003); however, due to the high individual variability existing between humans, the pharmacokinetics of catechins may change considerably from person to person (Ullmann et al., 2003). There is a large agreement between researchers in sustaining that catechins have a positive impact on human health. Evidence suggested that the regular consumption of catechins could contribute to prevent gain of weight or the onset of chronic disease such as T2D or metabolic syndrome (Thielecke al important hydroxycinnamic acids, such as cinnamic acid, pcoumaric acid, ferulic acid, caffeic acid, chlorgenic acid, and rosmarinic& Boschmann, 2009; Park, Bae, Im, & Song, 2014). In particular, catechins contribute to reduce glycaemia, enhance insulin sensitivity, decrease blood lipids, and reduce white fat al important hydroxycinnamic acids, such as cinnamic acid, pcoumaric acid, ferulic acid, caffeic acid, chlorgenic acid, and rosmarinicdepots.

Cinnamic acid improved glucose intolerance and insulin resistance in streptozotocin (STZ)-induced diabetic rats (Kasetti, Nabi, Swapna, & Apparao, 2012). Ferulic acid reduced blood

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glucose level and increased blood insulin level in several diabetic animal models (Jung, Kim, Hwang, & Ha, 2007; Ohnishi et al., 2004). Ferulic acid also increased glucokinase activity (Jung et al., 2007) and decreased glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activities in liver (Son, Rico, Nam, & Kang, 2011). Caffeic acid has been studied extensively in experimental diabetes and related complications. Caffeic acid shows hypoglycemic effects (Celik, Erdogan, & Tuzcu, 2009; Jung, Lee, Park, Jeon, & Choi, 2006), improves insulin level (Cy, Mc, Kc, & Mc, 2010), and enhances glucose intolerance (Bezerra et al., 2012) in diabetic animals.

Chlorogenic acid is the major phenolic components in coffee, which evidently reduces the risk of type 2 diabetes. Chronic dietary chlorogenic acid consumption attenuated cardiovascular, liver, and metabolic changes (Bhandarkar, Brown, & Panchal, 2019). Chlorogenic acid was found to attenuate diabetic complications in animals such as retinopathy via inhibiting retinal neoangiogenesis (Mei et al., 2018) and sensorineural auditory function (Hong, Nam, Woo, & Kang, 2017). However, chlorogenic acid could lower the fasting plasma glucose and HbA1c levels during late diabetes in db/db mice (Jin et al., 2015), and there is no sufficient evidence that decaffeinated coffee-enriched chlorogenic acid can control blood glucose in animals (Faraji, 2018). Chlorogenic acid poorly inhibits carbohydratedigesting enzymes (Nyambe-Silavwe & Williamson, 2018) and weakly impacted the fasting blood glucose level and blood glucose levels in the oral glucose tolerance tests in kk-[a.sup.y] mice (Igarashi, Takahashi, & Sato, 2017). Chlorogenic acid supplementation in a high-fat diet does not protect against features of the metabolic syndrome in dietinduced obese mice (Mubarak, Hodgson, Considine, Croft, &Matthews, 2013).

Caffeoylquinic acids:

PTP1B is one the most promising targets to improve insulin sensitivity, and overcome insulin resistance in peripheral tissues (liver, muscle, and adipocytes) (Eleftheriou, Geronikaki, & Petrou, 2019). Interestingly, recent studies demonstrated that chlorogenic acid and some caffeoylquinic acid derivatives behave as noncompetitive inhibitor of PTP1B: among all

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caffeoylquinic acids resulted the most potent inhibitor, showing a Ki value of about 15 micromolar (Chen et al., 2014; Zhang et al., 2018). These data suggest that caffeoylquinic acids could be used to improve insulin sensitivity in obese or T2D subjects. In keeping with this hypothesis, it has been reported that treatment with chlorogenic acid enhances glucose uptake in both insulin-sensitive and insulin-resistant adipocytes (Alonso-Castro, Miranda-Torres, González-Chávez, & Salazar-Olivo, 2008). Finally, studies conducted on human volunteers showed that the long-term assumption of coffee or extracts rich in caffeoylquinic acids reduces levels of blood glucose, increases the insulin response (Reis, Dórea, & da Costa, 2018), attenuates hepatic insulin resistance (Lecoultre et al., 2014), reduces serum lipids, and favors a reduction of body weight (Martínez-López, Sarriá, Mateos, & Bravo-Clemente, 2019). Together, these evidences support the hypothesis that caffeoylquinic acids have a deep impact on energetic metabolism of humans and can explain why the extracts rich in these compounds are recommended by traditional medicine for treatment of diabetes and obesity (Spínola & Castilho, 2017; Xie et al., 2019).

Anthocyanidins:

Anthocyanidins have a phenolic hydroxyl structure and are a class of hydroxyl donors with strong free radical scavenging ability. Anthocyanidins could reduce blood glucose by enhancing the antioxidant ability of bio-organisms through upregulating superoxide dismutase (SOD), lowering serum malonic dialdehyde, and inhibiting increasing thiobarbituric acid reactive substances (Roy, Sen, & Chakraborti, 2008; Tsuda, Horio, & Osawa, 1999). In vitro experiments indicated that cyanidin-3-glucoside protected cells from high glucose-induced oxidative stress by activating of glutathione synthesis (Zhu et al., 2012). Islet β cells are very sensitive to oxidative stress due to low expression of antioxidant enzymes such as CAT, SOD, and GPx in islets (Evans, Goldfine, Maddux, & Grodsky, 2003). Anthocyanin-rich mulberry extract exerted oxidative stress on islet cells against hyperglycemia through AMPK/ACC/mTOR pathway (Yan & Zheng, 2017). Anthocyanidins could improve insulin resistance by regulating blood lipid through reducing the levels of cholesterol, triglycerides, and low-density cholesterol and increasing the level of apolipoprotein and high-density cholesterol (Shi, Loftus, McAinch, & Su, 2017). Anthocyanidin-enriched bilberry extracts improved insulin resistance in KK-Ay mice, and

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reduced total cholesterol and triglycerides in liver and serum (Takikawa, Inoue, Horio, & Tsuda, 2010). Pro-inflammatory factors such as TNF-α and IL-6 were found associated with insulin resistance (Guo et al., 2012). Studies also shown that Cyanidin-3-glucoside inhibited 3T3-L1 cell adipocytes, activated insulin pathway via FoxO1, and inhibited TNF-α-mediated insulin resistance (Guo et al., 2012). Anthocyanins promoted insulin secretion in many ways (Rosanska & Regulska-llow, 2011). Cyanidin-enriched purple potato extract promoted insulin secretion by upregulating the expression of intracellular Ca2+ signaling pathway and glucose transport-related gene (Glut2) in mouse islet beta cells (INS1) (Sun, Du, Navarre, & Zhu, 2018). Anthocyanidins (delphinidin 3-arabinoside) in fermented berry beverages regulated DPPIV and its substrate GLP-1, increased insulin secretion, and upregulated mRNA expression of insulin receptor-related genes (Johnson & Mejia, 2016). Delphinidin 3-rutinoside could induce GLP-1 release via a calcium-dependent kinase pathway (Kato, Tani, Terahara, & Tsuda, 2015).

The most important findings from our study suggest that the intake of polyphenols may modulate the FG level and weakly affect the HbA1c amount. As it was shown above, total polyphenol consumption influences FG but not significantly. Nevertheless, in the group with high intakes of flavonoids (the main group of polyphenols), the glucose concentration was significantly lower compared to the group characterised by low flavonoid intake . The analysis of the association showed that polyphenols, especially flavonoids, influence the fasting glucose concentration; a negative association was observed between glucose level and total polyphenol, flavonoid, flavan-3-ol and stilbene intake .Anthocyanins and procyanidins are considered as highly bioactive compounds and present in fruits, bark, leaves, and seeds of many plants and plant-derived food. Nabavi and coworkers reviewed the benefits of anthocyanins for diabetic retinopathy.The evidence suggests that the antioxidant and other bioactivities of anthocyanins can mitigate vision loss and retinal degenera-tion in diabetes. It is still unclear on the beneficial role of anthocyanins in diabetic patients who suffered from retinal complica-tions. Anthocyanins have minimal adverse effects, however, and could be good candidates for future clinical trials. González-Abuín et al. focused on the healthy protective effects of procyanidins on type 2 diabetes and insulin resistance. Procyanidins were found to improve the damage induced by the diet, thus improve glycemia and insulin sensitivity. Human studies, although limited, further

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support the hypoglycemic effect of procyanidins. Procyanidins have been found to target several tissues involved in glucose homeostasis. In insulin-sensitive tissues, procyanidins modulate glucose uptake and lipogenesis and improve their oxidative/inflammatory state, the disruption of which plays a key role inT2DM development. In pancreas, procyanidins modulate insulin secretion and production and -cell mass.

Curcumin

Curcumin is a natural compound extracted from the root of Curcuma Longa and is the main component of the Indian curry spice. Curcumin has been consumed in the traditional Asian medicine for centuries because of its anti-inflammatory properties. Curcumin has also an-tioxidant and anticarcinogenic effects (5-7). Its anti-cancer activity is mainly attributable to the inactivation of hypoxia-inducible factor-1(HIF-1), as curcumin is known to downregulate HIF-1α (8) and HIF-1β (9) and inhibit downstream actions, e.g. angiogenesis mediated by HIF-1. Also, it is able to selectively kill tumor cells or prevent tumorigenesis through interfering with many cellular pathways (6, 10). It represses nuclear factor-κB (NF-κB), inhibits adipogenic transcription factors and the cell cycle, and induces apoptosis (11-13). In colorec- tal cancer, curcumin treatment upregulates p53 expression (14). It has been reported that curcumin inhibits TNF-α-induced expression of Interleukin-1 beta (IL-1β),IL-6, and tumor necrosis factor (TNF-α) in human keratinocytes. It enhances the secretion of adiponectin (15), inhibits insulin-regulated glucose transporter 4 (GLUT4) translocation and glucose transport (16, 17). Some studies demonstrate that 10–25 μM of curcumin efficiently inhibited the differentiation of mouse adipocytes. In concentrations of 10–50 μM, curcumin is able to activate AMP-activated protein kinase (AMPK)(18) and it can also inhibit the activation of MAPK pathway, c-Jun N-terminal kinases (JNK), p38MAPK, and extra cellular signal-regulated kinases (ERK) in adipocytes (19).

Genistein

The isoflavone genistein is a naturally occurring phytoestrogen, which is particularly highly concentrated in soy and soy-derived products; its possible suitability as a pharmacological agent has been studied, as it has been illustrated that people in Asia consuming large amounts of genistein-rich soy products are seldom affected by prostate or breast cancer (104, 105) and Type

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2 diabetes (106). In hypoxic conditions, genistein has been shown to suppress the HIF1α expression, accumulation, and activation of ERK (107, 108). Also, genistein seems to provide a protective effect on myocardial and endothelial cells, as it activates the exocytosis of the cardioprotective neuropeptide calcitonin gene-related peptide. This is due to vanillin receptor 1(VR1)-mediated action, of which genistein is supposed to be a direct activator (109), apart from capsaicin and gingerol. , the effect of genistein on differentiation of adipocytes has been illustrated with inconsistent results; this is in part due to contradictory actions of genistein with respect to applied concentrations (110, 111, 113-119). In a study, streptozotocindiabetic rats that received a daily intraperitoneal injection of 1 mg/kg bw showed a hypoglycemic effect (120). In a study on mice, 2 and 4 g genistein/kg diet significantly decreased fat pads, cholesterol, and lipid levels. Moreover, it inhibited mRNA expression of PPARγ, leptin, and TNFα and also increased mRNA expression in case of PPARα, AMPK, and adiponectin in adipose tissue (121). Furthermore, it enhanced the expression of genes involved in fatty acid oxidation, and at the same time, activated expression of UCP2, which mediates proton leakage by uncoupling ATP synthesis. This lowered metabolic efficiency may also account for the reduced fat accumulation and weight gain in animals receiving a daily genistein dose of about 200, 400, or 800 mg/kg of the body weight (Pandey et al., 2010). Similar to resveratrol, genistein administration decreased the ATP level in adipocytes (Pandey et al., 2010). Recent clinical trials on genistein in males showed an increase in adiponectin levels and a decrease in cholesterol and insulin levels, with doses that can easily be obtained by a soy rich diet. Table 6 displays recent clinical trials testing genistein with respect to diabetic and inflammatory markers.

Adipocytes are the place for energy storage and they produce cytokines including interleukin IL-1β, IL-6, TNF-α, MCP-1, leptin, adiponectin, and many other molecules; thereby, they are referred to as adipokines. In the context of inflammation, the adipose tissue is infiltrated through macrophages, and it also releases proinflammatory mediators, produces reactive oxygen species, and stimulates T-cell responses for successful defense against invading organisms.

DIETARY POLYPHENOLS, THEIR CHEMISTRY AND SOURCES

Polyphenols are found naturally in fruits and vegetables such as cereals, pulses, drtea, cocoa, coffee and so on (Arts and Hollman, 2005; Scalbert et al., 2005). Polyphenols are classified into

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different groups depending on the number of aromatic (phenolic) rings they contain and the structural elements that connect these rings. They are broadly grouped into phenolic acids, flavonoids, stilbenes and lignans (Khan et al., 2021). Plant derived polyphenolic compounds (for example, phenolic acids and flavonoids) occurs in conjugated forms with one or more sugar residues (as glycosides) bound to hydroxyl groups through direct linkages of the polysaccharide or monosaccharide-like sugar to an aromatic carbon (Rudrapal and Chetia, 2017). It is naturally bound to a variety of other molecules, including carboxylic and organic acids, lipids, amines, and other phenolic compounds (Kondratyuk and Pezzuto, 2004)ied legumes, spinach, tomatoes, beans, nuts, peppermint, cinnamon, pears, cherries, oranges, apples, red wine, tea, cocoa, coffee and so on (Arts and Hollman, 2005; Scalbert et al., 2005). Anthocyanidins are the bright coloured (blue, red, or purple pigments) flavonoid compounds found in the flowers, fruits and leaves etc.

Diabetes Mellitus Abnormality in glucose metabolism leads to hyperglycemia and consequently diabetes mellitus (type-1 and type-2). Apart from co-morbidities like heart disease or stroke, chronic complications may develop in diabetes such as diabetic retinopathy affecting eyes cause blindness, nephropathy altered renal functions, and neuropathy causing nerve damage and numbness/paralysis (Rizvi and Zaid, 2001; Rizvi and Zaid 2005; Junejo et al., 2017; Junejo et al., 2018; Junejo et al., 2020a; Junejo et al., 2020b; Hussain et al., 2021; Junejo et al., 2021). Apigenin derivative possesses strong antidiabetic activity extending protection against the variations throughout OS in diabetes (Junejo et al., 2021). Quercetin decreases lipid peroxidation and inhibits cellular oxidation in diabetes (Pandey and Rizvi, 2009). Resveratrol prevents cytotoxicity and OS caused by excessive glucose levels. Resveratrol decreases diabetes-induced kidney alterations (diabetic nephropathy) and thereby increases renal disorder and OS in diabetic rats. Resveratrol reduces secretion of insulin and deferrers insulin resistance onset which may be due to the inhibition of K+ ATP and K+ V channels in β cells (Chen et al., 2007; Oyenihi et al., 2016). The polyphenols of Hibiscus sabdariffa weaken diabetic nephropathy in terms of serum lipid profile and kidney oxidative markers (Lee et al., 2009). H. sabdariffa also contains flavonoids, protocatechuic acid, and anthocyanins..

CONCLUSION :

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Food phenolics are gaining importance in research as they have the potential to improve human health. Over 8,000 polyphenols have been reported from plants, and several hundreds of dietary polyphenols have been found in foods. Owing to their potent antioxidant capacity because of the presence of hydroxyl groups in their structures, polyphenols can effectively scavenge ROS and thus fight against OS induced pathological conditions or human diseases. Evidence from diverse in vitro studies discussed here supports that dietary sourced polyphenols plays a potential protective role in the prevention of neurodegenerative diseases, CVDs, diabetes, cancer, inflammation-related diseases, and infectious illness. However, prospective further research with adequate pre-clinical and clinical investigations could lead to the development dietary polyphenolic compounds as potent therapeutic candidates against various chronic human diseases.

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