Research Article

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Role of Nanoparticles against Diabetes Mellitus and Cancer

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Abstract

According to WHO, there are about 422 million diabetes patients throughout the world. Diabetes Mellitus is a metabolic disorder that results from hyperglycemia due to abnormal secretion and action of insulin. Diabetes is characterized into type 1 diabetes, type 2 diabetes and gestational diabetes. According to the survey of WHO in 2017, there are 3.2 million people suffering from cancer and 8.8 million deaths from cancer around the globe. About 90-95% cancer is due to lifestyle factors. There are six major indications of cancer that required forming a malignant tumor. Treatments based on nanotechnology, such as the creation of nanoscale medication delivery, can enable accurate cancerous tissue targeting while minimizing adverse effects. Nanoparticles can easily overcome cell barriers due to their biological composition. Although numerous treatments can be used to treat tumors, their sensitivity often results in insufficient outcomes and can cause a variety of adverse effects, including damage to normal cells.

Keywords: Nanoparticles; Cancer; Diabetes; Malignancy

Diabetes Mellitus

Economic and social status play an important constituent element in the determinants of health Deprivation is linked with reduced life expectancy and high morbidity, especially cardiovascular mortality [1]. Substantial social-economic gradients have been shown in the frequency of various causes for cardiovascular disease, along with diabetes [2]. Diabetes can be two or more times higher in low-income families in comparison to rich populations [3].

Rare and ethnic minorities carry a disproportionate burden of diabetes epidemics; have greater rates of prevalence, poor control of blood sugar, and complications [4]. Diabetes linked with the endocrine system illness caused the elevated blood sugar and the damage of different normal body tissue [5]. Diabetes is a multifactorial disease that has affected the lives of many people in this modern era. Different treatments of diabetes are present but in the last three decades, the outcome of these treatments in patients is still not perfect despite significant advances in the treatment of diabetes [6].

According to WHO, there are about 422 million diabetes patients throughout the world. Diabetes Mellitus is a metabolic disorder that results from hyperglycemia due to abnormal secretion and action of insulin. Diabetes is characterized into type 1 diabetes, type 2 diabetes and gestational diabetes [7].

The increasing prevalence of obesity is mainly responsible for the growing cases of diabetes. Different treatments are available for diabetes, but these drugs are required on regular basis to control the level of diabetes. Increased level of diabetes results in the damaging of blood vessels, cardiovascular diseases with increased risk of heart attack and kidney diseases.

Nanoparticles have the ability to inhibit the α-glucosidase (antidiabetic activity) and kill the cancerous cells (cytotoxic activity). Nanoparticles are of the size of 1-100nm and are made up of different metals. Physical, chemical, and biological processes have all been used to produce NPs. The disadvantages of the physical and chemical methods are the large amount of intensity required to meet the high temperature and pressure required for the synthesis of NPs as well as the toxic by-products that must be released into the environment.

The goal of this research is to utilize the yeast *Saccharomyces cerevisiae* to mimic the production of MgO nanoparticles and to analyze its antidiabetic and anticancer activity. A large number of microorganisms are able to synthesize Ag-NPs, ZnO Nps, MgO NPs extracellularly, the most important of which are *Cladosporium cladospo-rioides, Aspergillus clavatus, Fusarium oxysporum, Aspergillus fumigatus, Bacillus licheniformis, Fuserium semitectum, Penicillium brevicompactum,* and *Klebsiella pneumoniae.* The biogenic production of MgO NPs using *S. cervisiae* extracellular extract has never been described before. As a result, this novel study investigates the efficient production of MgO NPs utilizing a S. cerevisiae extracellular extract.

Etymological background of diabetes

The phrase **"Diabetes Mellitus"** comes from two different sources one from Greek that means "to pass through" and the second word "Mellitus" define the "sweet". It is thought that Greek give this word to disease to excess release of sugar through urine. The oldest way to detect diabetes in Chinese was the visual observation of identifying ants on the urine due to high sugar concentration in urine. Later on, western docs confirm this by themselves tasting the urine sample.

History

Diabetes has been observed and detected a long time ago however, its remedies were recognized in the Middle century. For a long time type II diabetes mellitus remain undiagnosed and complete amplification become into account in twentieth-century [8]. In 1889 two colleagues Joseph Von Mering and Oskar Minkowski describe the vital role of pancreatic beta cells in diabetes. They did an experiment on dogs by completely removing the pancreas of dogs and they observed them with diabetes which died after some time of diabetes induction. In 1910, Sir Edward Albert Sharpey-Schafer, at Edinburgh in Scotland clarify so desire of diabetic patients is a single chemical that is generally produced by the pancreas later on it is named as insulin hormone [9].

After some time Frederick Grant Banting and Charles Herbert repeated the same work of removing the pancreas as early performed by Von Mering. And they found that by removing the pancreas, body cannot produce insulin and become diabetic however, they reverse the experiment by giving artificial insulin to the dogs by extracting the insulin from the pancreas of healthy dog. It proves as a big success in the understanding and treatment of diabetes and also helps in understanding the role of the pancreas in metabolic activities [10]. Different scientists continue the extraction of insulin from the pancreatic cells of at the University of Toronto in Canada, and it became a proper cure for diabetes becomes into account and in 1922 for the first time a person was handled by giving extracted insulin. Sir Harold Percival (Harry) Himsworth in 1935 make a difference between type I and type II diabetes [11]. The standards for the prognosis of diabetes is devised by WHO (World Health Organization) is proven in desk below [12].

Table 1.1 Diagnosis standards for diabetes in keeping with WHO

Status	Fasting blood glucose level	Oral glucose tolerance test
(2-hour plasma glucose)	68	59.1
Normal	110mg/dL (< 6.1 mmol/L)	140mg/dL (< 7.8 mmol/L)
Diabetes	126 mg/dL (≥ 7.0 mmol/L)	200mg/dL (≥11.1 mmol/L)

Role of insulin in diabetes mellitus

Insulin is a polypeptide hormone processed inside the beta cells of the Langerhans islets in the pancreas in humans and different mammals. The endocrine section of the pancreas is designed by means of the islets of Langerhans, accounting for two sections of the complete pancreas mass, with beta cells representing 60 to 80 percent of all cells of the islets of Langerhans [13]. With liver, muscle, and adipose tissue being the most necessary goal organs for insulin action, insulin famous a multitude of outcomes in many tissues. Promoting the production of carbohydrates, proteins, lipids, and nucleic acids is the primary physiological characteristic of insulin. The incentive of glucose transport throughout muscle and adipocyte cell membranes, legislation of hepatic glycogen synthesis, and restriction of glycogenolyses and gluconeogenesis are between outcomes of insulin on carbohydrate metabolism [14].

Overview of pancreas

A discount in blood glucose attention is the end result of these activities. Insulin promotes the transmission of amino acids throughout membranes about protein metabolism, stimulates protein synthesis, and inhibits proteolysis. Insulin is influenced through the incorporation of fatty acids from circulating triglycerides into adipose triglycerides and lipid synthesis; lipolysis is inhibited. By enhancing the production of ATP, DNA, and RNA, insulin leads to nucleic acid [11]. By binding to an excessive compatibility particular receptor positioned on the plasma membrane, insulin initiates its physiological effects. The receptor is saturable, and at plasma insulin awareness of 20-30 µU/ml, each binding ability and organic recreation of insulin are maximum. During the binding process, insulin is no longer altered, and the disulfide bond response is now not involved. After binding to the receptor, thru a 2d messenger that influences enzymatic progressions, to the interior of the cell, signals transfer by insulin. The hormone is consequently possibly to raise out its movements barring coming into the cell to two membrane-bound enzyme systems: the adenyl cyclase-cAMP and the Magnesium-activated Sodium-Potassium-ATPase systems. Insulin inhibits the formation of cAMP solely in conditions the place catecholamines, glucagons, or different hormones have previously inspired it. Intracellular potassium transfer stimulation is one of wider outcomes of insulin [15].

Potassium, in turn, is a tremendous aspect of membrane possibility and enzymatic regulation. Many intracellular enzymes activation entails magnesium. The accumulated intracellular magnesium is additionally stimulated through insulin. It's been endorsed that the receptor of the insulin membrane is in the locality of the sodium-potassium-ATPase magnesium-dependent gadget and that receptor activation enhances the undertaking of system. As a result the intracellular accretion of magnesium with the activation of integral intracellular enzymes. The everyday plasma insulin awareness at eight am is 5 to 15 µU / ml following a single-day fast. Postprandial values can be 5-10 instances more than the baseline, one hundred g glucose. The output of Insulin is about 0.5-1.0 U/h beneath the basal situation and will increase about 5 instances after ingestion of meals [16]. A basic advance in keeping up glucose homeostasis and clearing the postprandial glucose load is the capacity of insulin to encourage tissue glucose take-up [17]. The creation of insulin is straightforwardly corresponding to the amount of sugar (starches) burned through. The more sugar one chomps, the extra insulin the body should create, yet this degree of insulin has never been delivered by the minuscule pancreatic beta cells. With a restricted ability to create insulin, a limit that under ordinary dietary conditions are all that anyone could need to endure forever, automatic insulin over-creation will in the end debilitate that limit and the cells will stop working.

Symptoms

People having diabetes face specific signs of uncontrolled diabetes which includes

- weight loss
- polyuria
- increased thirst
- extended starvation

Several different non-specific signs can additionally be discovered in humans which include blur vision, fatigue, headache and gradual healing after cuts. Prolonged excessive sugar degree can lead to glucose absorption into the lens of the eye that affects imaginative and prescient changes. A few pores and skin issues can additionally be skilled due to diabetes. Type 1 diabetes additionally journey many signs consisting of ketoacidosis (abnormal pain), respiratory scent and diminished degree of consciousness. An extreme opportunity additionally consists of dehydration [18].

Application of nanoparticles

Nanoparticles are used in various fields of life. Nanomaterials hold immense promise for significantly improving existing diagnosis, therapy, and designing novel approaches to treat a variety of human ailments. Nanotechnology may be able to create many new materials and devices, with a vast range of applications, such as in medicines, electronics, biomaterials, and energy production as shown in (Figure 1.1).

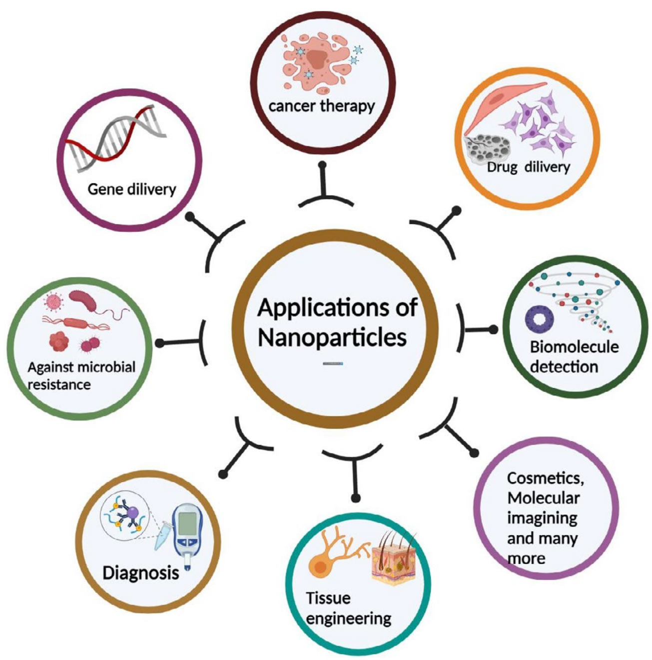

Figure 1.1. Application of nanotechnology in various fields of science

Role of Nanotechnology in Diabetes Mellitus

In the 21st century, nanotechnology is a new important technology. To manufacture materials this technology uses single atoms and molecules. It investigates the properties and application of material that structure size varying from 0.1-100 nm. In the receptor, they can protect the drug from the enzymes decomposition and then other methods of administration make the local drug concentration greater, so it can enhance the efficiency of drugs and reduce side effects.

Microbes are true pathogens and should be removed from the list of beneficial microorganisms. *Saccharomyces cerevisiae*, also referred to as "baker's yeast," can be found in different environments. *S. cerevisiae* is most known for its role in bread, beer, and wine fermentation, both traditional and industrial. It can also be used as a nutrition supplement and to treat antibiotic-related diarrhea *Saccharomyces cerevisiae* infections in man [19].

Cases of confirmed *S. cerevisiae* infections have risen in recent years, possibly because of the rising number of immunosuppressed patients and advancements in diagnostic procedures. S. cerevisiae, on the other hand, has long been thought to be a nonpathogenic and safe organism [20]. Because of its basic properties and applicability in various fields of physics, chemistry, and nanotechnology, MgO nanoparticles (MgO NPs) have received a lot of interest. MgO nanoparticles can be utilized as a catalyst (Di Cosimo et al., 2014) antibacterial agent [21], biodiesel production [22] and optoelectronic devices [23], and the latest research review finds that nano MgO is a heterogeneous catalyst and it has gotten a lot of interest because of its low-cost non-toxic catalyst and environmental compensation. The effectiveness of MgO Nps is determined by their size, physical aspects, and chemical characteristics [24]. The use of nano-synthetic methods results in technological and environmental issues. To solve this challenge, we need a new nanoparticle synthesis process that reduces harmful pollutants. This study elaborates on the biogenic synthetic approach using non-toxic precursors.

Cancer

The classical concept of cancer is “wounds that never heal” or “the organs that never develop” due to certain limitations. This idea of carcinomas is very helpful for understanding the inflammatory & developmental signaling between activated tumor microenvironment and cancer cells. Cancer cells have a tendency to spread and invade adjoining cells of the body. The human body composed is of millions of cells, under normal conditions these cells grow, divide and die in a conventional manner. Due to certain abnormalities, these cells grow uncontrollably, forming malignant tumors (neoplasm) that grow beyond their usual boundaries and spread throughout the blood stream in the human body [25].

According to the survey of WHO in 2017, there are 3.2 million people suffering from cancer and 8.8 million deaths from cancer around the globe. About 90-95% cancer is due to lifestyle factors [26]. There are six major indications of cancer that required forming a malignant tumor. These are

- Sustained angiogenesis
- Abnormalities in programmed cell death (apoptosis)
- Inhibition of anti-growth signals
- Migration and invasion of tissue
- The indefinite replicative potential of cells
- Self-stimulation of growth signals
- Tumor formation from a normal cell is a multistage process that is known as a malignant progression [27].

Cancer Prevalence

Cancer is the third major reason for death around the globe. According to IARC (International Agency for Research on cancer), in 2018 almost 9.6 million people were died because of cancer [28]. Due to the present situation it is projected that by 2030, 17 million cancer death and 26 million new cancer cases will be appeared per year [29].

In LMIC (low-and middle-income countries), deaths rates are expected to grow rapidly as the population grow, adopted lifestyle behaviors such as tobacco use, physical inactivity and reproductive patterns increase the cancer risk factors [30].

General Indications of Cancer

General symptoms and signs aren’t really precise, when cancer begins, it produces no symptoms. It relies on a specific form, locality and grade of cancer. Few symptoms are specific e.g.

- Weight loss
- Lumps
- Tissue masses
- Persistent cough
- Fatigue
- Skin changes
- Unorthodox bleeding
- Change in body organ function (bowel or bladder)
- Voice change or pyrexia.

People may become anxious or depressed post-diagnosis. In general, cancer patients also have a greater risk of suicide due to significant psychological, physical and social impairments. It is higher especially in those adult patients that are survivors of childhood cancers. In such patients, the risk of suicide is approximately double

Two symptoms of cancer are as following

- Local symptoms
- Systematic symptoms

Risk Factors and Causes of Cancer

By changing lifestyle cancer can be prevented. Approximately 90-95% of cancer problems are due to mutation in genes due to environmental factors [31]. There are many causes of cancer, some are preventable and some are not preventable factors [32].

Preventable risk factors are
• Alcohol and tobacco use
• Excessive body weight
• Infection
• Radiation
• Hepatitis B & C and some HPV increase risk of liver and cervical cancer Not preventable causes are
• Age
• Autoimmune diseases
• Genetics

Detection and Diagnosis
The mortality rate can be compressed if it is diagnosed and handle early. People with cancer are investigated by the appearance of signs or symptoms with medical tests [33]. Doctors classify cancer by:
• location in the body
• tissues that it forms in
• medical test

Some of these tests includes
• MRI & Ultrasound
• Endoscopy
• Biopsy
• Radionuclide scanning (to visualized lymph nodes)
• Mapping and sequencing of the human genome

Cancer Treatments
Innovative research has fueled the development of treatment technologies and new medication. It requires a specific treatment after correct diagnosis. Oncologist usually prescribes treatments based on the person overall health, its stage and cancer type. The main intention is the cure to spread cancer, improve the condition of a patient's life and prolong life. This can be achieved by palliative or supportive care, psychosocial support and good medication [34]. Below is some cancer treatment:

• Chemotherapy
• Radiation
• Immunotherapy
• Alternative medicine
• Stem cells transplant
• Angiogenesis inhibitors [10].

Although cancer is incurable, but early detection and timely action of treatment can cure this disease to some extent. Delay in treatment is very lethal and causes the death of a person [35].

Role of Nanoparticles for Cancer treatment
Throughout the years, development in both polymer and nanoparticles chemistry has made it possible to synthesis and conjugation of functionalities that can react to stimuli. This is a significant advancement in cancer treatment since it allows for not only a passive targeting strategy but also passive targeting using carrier monoclonal antibody conjugates that can be triggered at any time/site.

Treatments based on nanotechnology, such as the creation of nanoscale medication delivery, can enable accurate cancerous tissue targeting while minimizing adverse effects. Nanoparticles can easily overcome cell barriers due to their biological composition. These nanostructures have been employed in the treatment of cancerous cells for many years due to their active and passive targeting capabilities [36]. Although numerous treatments can be used to treat tumors, their sensitivity often results in insufficient outcomes and can cause a variety of adverse effects, including damage to normal cells [37].

MgO nanoparticles synthesized from yeast Saccharomyces cerevisiae having the ability to kill the cancerous cells with a significant reduction in toxicity to normal cells. Nanomaterials are also being studied for their potential applications in intracellular delivery of DNA, RNAi, proteins, peptides, and tiny medicines to induce cancer cell death, as contrast agents for cancer imaging, and platforms for targeted gene and chemotherapeutics delivery to tumor locations [38].

Diabetes Mellitus
An inherited disease caused by elevated blood glucose levels, or by the improper secretion of insulin hormone is called diabetes mellitus. As a consequence of the defect, abnormal carbohydrate metabolism, and elevated blood glucose levels can lead to organ damage and immunological reactions that may affect the pancreatic beta cell damage. The increased production of cytokine may lead to insulin resistance [5].

The world is persistently battling against diabetes since years. Besides all the advancements in therapeutic treatment, diabetes is still the fifth leading cause of death all over the world. The spread of diabetes has a growing trend due to aging, change in lifestyle, nutrition and lack of exercise. Several genetic elements and other behavioral, temporal and environmental factors may also contribute to the spread of this disease [39].

Diabetes is an endocrine system disease and according to the Global Systematic Search of published studies. According to the estimated ratio, 500 million people are affected by Type II diabetes in the surrounding world. The prevalence rate is elevated among developed and under-developed countries and will tend to increase in all countries covered by the estimated period, but the highest diabetic ratio is observed in under-developed and developing countries [40]. Its prevalence (Fig.1) is considered to be high in the adult population all over the world (4.7% in 2014 to 8.8% rise in 2017 and predicted to get elevated up to 9.9% in 2045) [41]. It is predicted by International Diabetes Federation (IDF) that by 2025, diabetes will affect 11.5 million people in Pakistan which made Pakistan the 5th most affected country on IDF classification of the diabetic population [42].

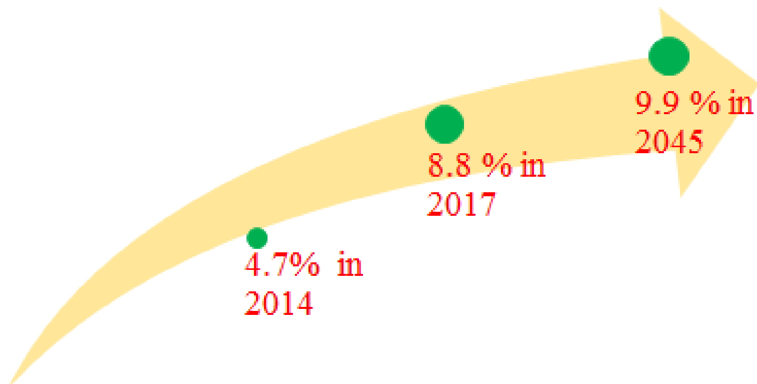

Figure 2.1. Prevalence of DM by WHO report

Types of Diabetes Mellitus

Based on insulin secretion diabetes can be classified into three groups;

Type I (Insulin –dependent diabetes mellitus)

Type I diabetes (T1DM) is a condition for chronic autoimmune diseases that leads to a serious shortage of pancreatic insulin production, Therefore, it is necessary to give regular and proper insulin to prevent hyperglycemia, metabolic compensation, and life-threatening chronic ketoacidosis (DKA). At any stage of life Type I diabetes can occur [43].

Type II (Noninsulin-dependent diabetes mellitus)

It has been well constituted that there is a long-term prodromal stage prior to clinical diagnosis of Type II diabetes mellitus, consisting of progressive plasma glucose uptake (PG) within the range of non-diabetes, weight gain and insulin sensitivity weakening (Si). Generally, such irregularities can be detected 10 years before the diagnosis of diabetes [44]. The various factors responsible for elevated blood glucose level (hyperglycemia) involves are shown in Fig. 2.2.

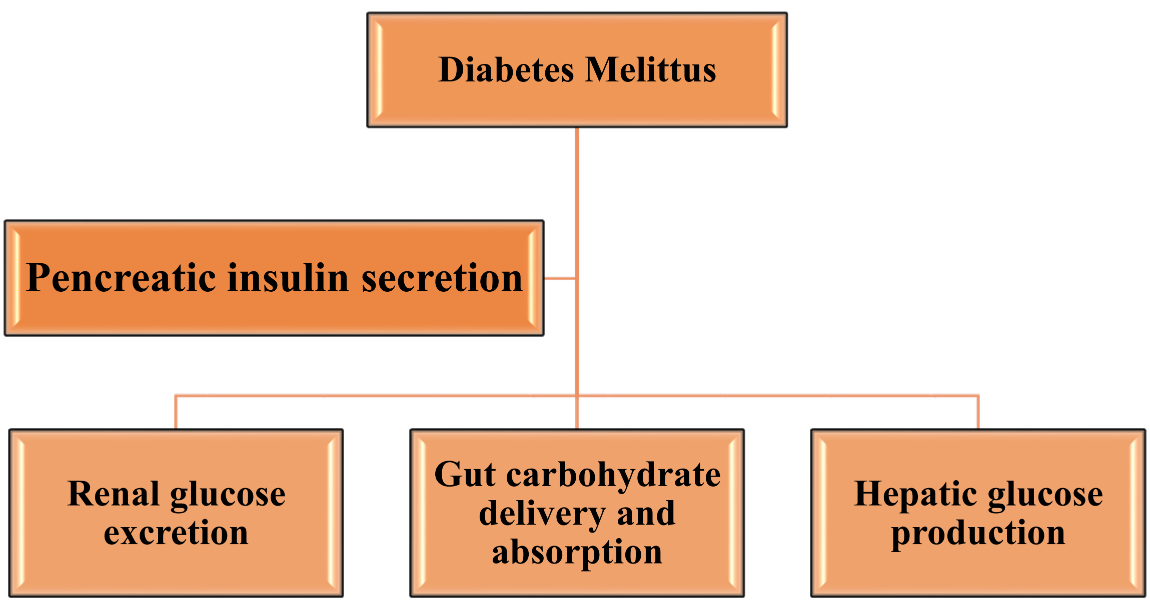

Figure. 2.2. Factors responsible for the elevated blood glucose level in DM.

As per reports by the National Institute of Diabetes and Digestive and Kidney Diseases, it is the most common type of diabetes and it is highly coupled with obesity. A person facing this problem is not insulin dependent. Sometimes insulin level in serum is elevated, other times normal or depressed. The most common diabetic obstacles begin after 40 years [45].

Other Types of Diabetes

In exceeding less frequent type of diabetes, gestational diabetes occurs in the course of pregnancy [46].

Maturity-Onset Diabetes of the Young (MODY)

MODY is an unprecedented form of diabetes wherein mutation in only one gene can affect glucose concentration. 1-2% of patients are diagnosed with this type of diabetes [47].

Gestational diabetes

Gestational Diabetes (GDM) is spreading along with a symbolic overweight and obesity becoming more prevalent among pregnant women around the world. There are multiple factors such as nutrition, obesity, family history, and ethnicity which are related to the unnecessary weight gain associated with gestational diabetes. There is a high risk of maternal and fetal morbidity and mortality associated with Poor control of Gestational Diabetes. Early diagnosis and narrow control of blood sugar provides an opportunity to improve maternal and fetal health [48].

A diabetic patient has to face both conditions includes improper insulin secretion and imperfection in insulin action. As a consequence blood sugar level is elevated. Symptoms of elevated blood sugar level are significant weight loss, blurred vision, renal failure and cardiovascular diseases [49]. A combination of lifestyle changes and therapeutic treatment is necessary for achieving good metabolic control of diabetes metabolism and keep it in the long term. To carry the normal level of blood sugar, inhibit the risk of macrovascular and microvascular complexity. There are different oral and injectable treatments available for the diabetes mellitus at the present time [50].

Understanding of diabetes should be based on its genetic basis. Therefore, with the first type of diabetes, there is a strong lack of insulin secretion, currently available treatment is insulin or analog insulin delivery. However, type II diabetes is a much more complex disease in which insulin resistance prevails in the early stages. In advanced stages, insulin resistance still exists, but there is a clear absence of insulin secretion. Therefore, the therapeutic treatment should be based on the stage of disorder and the characteristics nature of the patient [51]. Diabetes is a multi-factorial disease that has affected the lives of many people in this modern world. Worldwide diabetes is known to be the fifth major cause of death [52]. Today, there are various treatments available for the control of diabetes such as insulin therapy, pharmacotherapy, and diet therapy etc. In the last three decades, the outcome of these treatment in patients are still not perfect despite significant advances in the treatment of diabetes.

Disadvantages of treatments include:

- Drug resistance
- Side effects
- Toxicity

Today, nanoparticles are used for various treatments due to their limited side effects and better efficiency [53]. With cell biomolecules at Nano scale, material's reduction may also change its properties, in a specific way capable them to interact. Nanoparticles (NPs) for delivery to target cells are loaded with therapeutic agents [54]. As compare to mineral salts, metal nanoparticles are seems to be less harmful, and on the organism have multifunctional effect [55]. Some nanoparticles have Anti-hyperglycemic effects that often due to their ability to improve the pancreatic tissue's activity, this activity is achieved by increasing insulin secretion or by reducing intestinal glucose absorption [56].

Advancement in the field of nanotechnology gain new insights into its various applications in treatment of many diseases counting diabetes mellitus [57]. Nanotechnology is an attractive field of research relating to the production of variable size nanoparticles, form and chemical composition, with controlled dispersion [58].

Biological, physical, and chemical approaches are being utilize for synthesizing nanoparticles [59]. In Biological methods, yeast extracts are used for the production of nanoparticles which are more environment-favorable as compared to the chemical and physical method [60]. Advancement in the field of research, yeast-based nanoparticles are used for the treatment of diabetes mellitus which are target specific and shows better efficiency and limited side effects due to the presence of the natural compounds and anti-diabetic activity [61].

Nanotechnology enabled the production of silver nanoparticles from natural materials that were potent inhibitor of α-glucosidase enzymes in the treatment of diabetes mellitus [62]. The glucose metabolizing enzymes α-glucosidase and α-amylase were inhibited by the produced silver nanoparticles from *Allium cepa*, resulting in a significant antidiabetic action [63].

The advancement of nanotechnology has allowed many materials including ZnO NPs are now being evaluated for biological uses and disease-modifying therapies. According to this study, ZnO NPs can target a number of different hallmarks of DM. As a result, ZnO NPs are a promising anti-diabetic agent that warrants additional research and clinical testing [64].

Table 2.1. Different nanoparticles that are involved in the treatment of diabetes mellitus (inhibition of α-glucosidase and α-amylase).

Sr. No	Source	Family	Size (nm)	Nanoparticles	Inhibition of enzyme	References
1	*Halymenia poryphyroides*	*Halymeniaceae*	34 to 80	Ag NPs	α-glucosidase and α-amylase	(Manam et al., 2013).
2	*Tephrosia tinctoria*	*Fabaceae*	73	Ag NPs	α-glucosidase and α-amylase	(Sharma et al., 2017).
3	*Aspergillus niger*	*Trichocomaceae*	5 to 100	CuO NPs	α-glucosidase	(Noor et al., 2020).
4	*Padina boergesenii*	*Dictyotaceae*	80	Au NPs	α-glucosidase	(Senthilkumar et al., 2015)
5	*Nigella sativa*	*Ranunculaceae*	20 to 30	Au NPs	α-glucosidase and α-amylase	(Veeramani et al., 2021)
6	*Cladosporium species*	*Davidiellaceae*	24	Ag NPs	α-glucosidase and α-amylase	(Popli et al., 2018)
7	*Capsicum frutescens*	*Solanaceae*	25 to 35	CuO NPs	*α-Amylase*	(Velsankar et al., 2021)
8	*Silybum marianum*	*Asteraceae*	33.6	ZnO NPs	*In-vivo studies*	(Arvanag et al., 2019)

Cancer

Cancer is a continual battle around the world. Cancer is a disorder that occurs when cellular changes throughout the body cause unrestricted growth and cell division. As a result of the unrestricted division, abnormal cells are formed. These cells are known as Cancer cells, Tumor cells or malignant cells. These abnormal cells have the ability to permeate normal body tissues and cause irregularities. Many types of cancer and abnormal cancer-causing cells are named after the tissue, from which these cells were originated (for example, breast cancer, lung cancer, colorectal cancer) (Divan & Royds, 2020).

There is another mechanism of cancer occurrence in which these abnormal cells can separate from that original cell mass, after traveling along the blood and lymph systems they settle in other organs where they can divide repeatedly. This process is called metastatic spread or metastasis in which cancer cells leave their native area and grows in another area of the body (Reddy et al., 2019).

According to research, there are two opposite explanations of the increasing incidence of cancer. Firstly, environmental pollutants can slightly contribute to total changes in cancer incidence, and thus increase in population size, aging and lifestyle such as smoking, alcohol, and nutrition contributes to cancer. There are several factors that affect the induction of cancer in humans (Figure 2.3). By contrast, another interpretation said that given arguments are insufficient, and states that besides these factors there is a contribution from the environment and forcible exposure to various physical, chemical and biological agents that may be present in the environment of the individuals play a major role in the dysfunctionality of the cells. Non-infectious diseases are now responsible for most of the world's deaths, and cancer is expected to be the leading cause of death worldwide (Grasgruber et al., 2018).

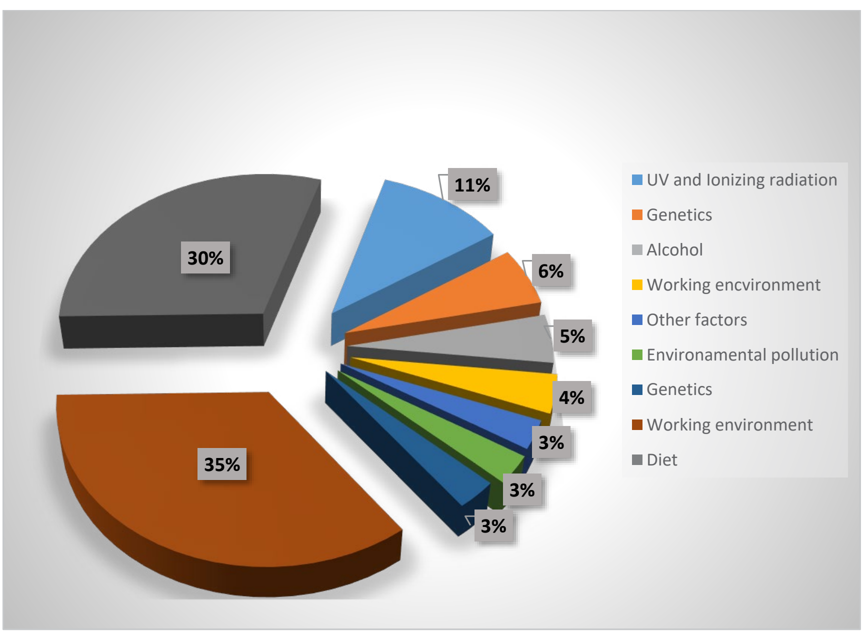

Figure.2.3. Factors affecting the induction of cancer in human

Especially for gastric, liver and cervical cancer, chronic infections by Hepatitis causing viruses (HBV, HCV), HPV and H. pylori are the principle causes. These all infections requires a considerable period of latency during which the infected agent stimulated inflammation, tissue damage, local repair and stem cell tissue must be activated until the pre-malignant or malignant lesions arise. It is recently discovered that activated mechanisms of innate anti-viral infection such as the ABOBEC family of antiviral proteins, over a long period of time can lead to somatic mutations in tumor cells. The other most important signature is one persistent with the APOBEC activation [68].

The reproductive organs or organs are involved in several major cancer exclusive or largely to one gender (cervix, prostate, breast, ovary). These tumors have a lot of hormonal impacts. Many breast cancers, for example are estrogen and or progesterone dependent, and this knowledge has aided both prevention and therapy. Many other forms, however, have a significant gender disparity: male bias in bladder cancer, any pediatric cancers, and liver cancer; female bias in chronic lymphocytic leukemia and thyroid cancer. In the vast majority of cases, we are unaware of these consequences. This is a crucial topic of cancer epidemiology since male and females hormone production and exposure alter considerably over time.

Many form of cancers are caused by chronic inflammation due to by irritants, toxins or immune inflammatory processes. For example, a person with colitis disease or Crohn's disease is more like to develop colorectal cancer [69]. The role of asbestos in lung cancer, Sun burn and UV radiation in skin cancer are well known. These cancer, like viral infections evolve over decade and the aspect of aging on the development of cancer due to inflammation is poorly understood.

It has been found by various studies that cases of cancer increase with the age as immune function declines. This phenomenon is called immune senescence [70]. In one study, it was shown that tumors have the ability to limit the function of CD8+ cells that also include specific reaction to tumor antigens, specific for prostate tumors. The intricate mechanisms causes to deteriorate cellular immunity are very unclear, but the gradual decline in thymic output of T cells results in immune senescence in old age. With age, the production of new naïve T cells reduces due to which T cells undergo repetitive cell division in order to maintain the status quo so that the T- cell compartment remains relatively stable in the overall size. This survival of the peripheral T cells results in defects in all types of activation states of T cells, from the naive to the terminally differentiated. This decrease in functional immunity may allow tumor growth and may even promote tumor formation by contributing to low- level inflammation. Specific cytokine blockers may be useful to both neoplasia and other inflammatory disease states in order to avoid this pro-inflammatory environment, but they have drawback of impairing the immune system [71].

According to a report in 2015 by World Health Organization (WHO), cancer is the first or second major cause of death before 70 years in 91 out of 172 countries, and occupies a third or fourth place in 22 additional countries [72]. The most common causes of cancer related deaths all over the world are:
- Lungs (1.76 million deaths)
- Colorado (862,000 deaths)
- Stomach (783 000 deaths)
- Liver (782 000 deaths)
- Breasts (627 000 deaths)

According to survey report on cancer in Pakistan major prevalence of cancer are:
- Oral cancer over all prevalence 9%
- Prostate cancer over all prevalence 5%
- Gastric cancer over all prevalence 6%
- Breast cancer over all prevalence 31%
- Colorectal cancer over all prevalence 5% [73].

Prevention from Cancer
Although, advancement in cancer treatment has not been as effective as other chronic diseases. Prevention from cancer is defined as effective measures to minimize the cancer risk by controllable life style, proper medication, healthy diet and vaccination [74].

Treatment of Cancer
The most recent available treatments of cancer are tumor surgery, chemotherapy, and radiotherapy [73]. Hormone therapy treatment is used for prostate cancer and breast cancer. In tumor surgery, aim is to remove tumors, tissues or areas with cancer cells, such as lymph nodes. Doctors can also do this to analyze the disease or determine the seriousness of disease? Three different kind of surgical treatments are:
- Laser surgery
- Electro surgery
- Cryosurgery

Innovative research has developed the treatments technologies and new medication. It requires a specific treatment after correct diagnosis. Oncologist usually prescribes treatments based on the person overall health, its stage and cancer type [75]. The main intension is cure to spread cancer, improve the condition of patient's life and prolong life. This can be achieved by palliative or supportive care, psychosocial support and good medication.

Below is some cancer treatment:
- Chemotherapy [75]
- Radiation
- Immunotherapy
- Alternative medicine
- Stem cells transplant
- Angiogenesis inhibitors [76].

Although cancer is incurable, early detection and timely action of treatment can cure this disease to some extent. Delay in treatment is very lethal and causes the death of a person [77]. Today, the use of nanoparticles for the treatment of cancer is getting more and more attention [78]. Because in chemotherapy, due to the non-selectivity of used medicine, large number of healthy cells are damages with cancer cells. The other available treatments are expensive, not widely available and limited by side effects followed by resistance to treatment [79].

Role of Nanotechnology in cancer treatment

As a result, nanomaterials with specialized properties can be used for biomedical research and applications in both vivo and in vitro, actively associated with cellular components or mimicking various chemical and biological molecules. The combination of nanotechnology with biology are beneficial for the development of diagnostic gadgets, contrast agents, drug delivery systems, and pharmaceuticals per se. Microorganisms biosynthesized nanoparticles by grabbing target ions from their surroundings and then converting the metal ions into the element metal using enzymes produced by cell activities. According to where nanoparticles are generated, it can be divided into intracellular and extracellular synthesis [80]. Drug carriers for targeted delivery, magnetic resonance imaging (MRI), cancer treatment and gene therapy and DNA analysis have all benefited from the biosynthesized nanoparticles. The interaction of inorganic molecules with living organisms as recently piqued the curiosity of scientists. Many microorganisms can create inorganic nanoparticles via intracellular or extracellular pathways according to research. These microbes includes yeast and fungus are involved in the biological production of various nanoparticles including gold, silver, alloy, magnesium and other metal nanoparticles, oxide nanoparticles consisting of magnetic and nonmagnetic oxide nanoparticles, sulfide nanoparticles, and other miscellaneous nanoparticles [81].

Microbes based products have bioactive components which have anti-diabetic and tumor inhibitory properties [82]. Microorganisms have chemo preventive and chemotherapeutic compounds that have more than one mode of action to suppress oncogenes [83]. These extracts when used for the formation of nanoparticles will enhance the suppression of oncogenes and will be readily available and inexpensive [84]. Similarly the targeted delivery of these chemicals to cancerous cells is another goal [85]. Nanoparticle synthesis from microorganisms is used to treat and cure cancer as they target cancerous cells only [86].

Table 2.2 Different nanoparticles that are involved in the treatment of cancer (different cancerous cell lines).

Sr. No	Source	Family	Size (nm)	Nanoparticles	Cancer cell lines	References
1	*Eriobotrya japonica*	*Rosaceae*	15-37	Ag NPs	MCF-7 and HeLa cells	(Jabir et al., 2021)
2	*Cucumis prophetarum*	*Cucurbitaceae*	30-50	Ag NPs	Breast cancer cell lines MCF-7	(Ezhilarasi et al., 2016)
3	*Moringa oleifera*	*Moringaceae*	5-100	NiO NPs	Human colorectal adenocarcinoma cell line HT-29	(Noor et al., 2020).
4	*Candida albicans*	*Saccharomycetaceae*	60–80	Au NPs	HeLa cells	(Chauhan et al., 2011)
5	*Escherichia coli and Staphylococcus aureus*	*Enterobacteriaceae and Staphylococcaceae,*	27	Al ZNO NPs	Epithelial, human breast cancer cell line MDA-MB231 cells	(Khashan et al., 2020)
6	*Solanum trilobatum*	*Solanaceae*	12.50-41.90	Ag NPs	MCF 7	(Ramar et al., 2015)
7	*Saussurea costus*	*Asteraceae*	30-34	MgO NPs	MCF-7	(Amina et al., 2020)
8	*Laurus nobilis*	*Lauraceae*	24	ZnO NPs	Human A549 lung cancer cells	(Vijayakumar et al., 2016)
9	*Lactobacillus Sp.*	*Lactobacillaceae*	13. 3	MgO NPs	Human Leukemia Cell Lines HL-60	(Mohanasrinivasan et al., 2018)
10	*cordia myxa L.*	*Boraginaceae*	40-55	CuO NPs	breast cancer lines AMJ-13,MCF-7	(Thamer & Barakat, 2019)

[87] demonstrated that silver nanoparticles have a significant effect on human cancer cell lines in MTT assay, although no cytotoxicity effect on normal cell lines. The biological synthesis of AgNPs with antibacterial and anticancer activity will help in the development of a symbiotic relationship between medical science and nanoscience to more effectively control deadly diseases [88]. Another study reported that The MgO nanoparticles synthesized from *Lactobacillus* sp. inhibit the growth of human leukemia cell lines HL-60, elucidating the potential of MgO nanoparticles for the therapy of leukemia.

Molecular docking

Molecular docking methodology explores the behavior of small molecules in the binding site of a target protein. As more protein structures are determined experimentally using X-ray crystallography or nuclear magnetic resonance (NMR) spectroscopy. Molecular docking is increasingly used as a tool to determine the binding sites of protein with ligand. Docking against homology-modeled targets also becomes possible for proteins whose structures are not known.

Over the last two decades, more than 60 different docking tools and programs have been developed for both academic and commercial, use such as AutoDock (Österberg et al., 2002), DOCK [89], GOLD [90], Surflex [91], FRED [92], FlexX [93], Glide [94], LeDock, ICM [95], LigandFit [89], rDock [96], UCSF Dock [97], LeDock [98], MOE-Dock [99], AutoDock Vina [100], and many others.

[101] reported to simulate the actual ZnO nanoparticles, changing the crystalline nature produced three distinct ZnO nanoclusters Z3, Z5, and Z7 with dimensions of 11 nm, 32 nm, and 49 nm. Mercury 3.8 version and Gauss View 6 software were used to create the clusters of nanoparticles. Z3 form three hydrogen bonds with the Aspartic acid (ASP 46) and Glycine (GLY 10), residues. The sample Z5 showed hydrogen bonds with glycine (GLY 10) and phenylalanine (PHE 1) residues. Whereas Z7 forms hydrogen bonds with the amino acids residues aspartic acid (ASP 46), Glutamic acid (GLU 286), and Valine (VAL 325).

Another study demonstrated that copper oxide nanoparticles(CuO NPs) showed strong binding interaction with the amino acids of protein (α-amylase) through Van der waal interaction including ASP 18, GLY 20, ARG 52, SER 53, ALA 110, TRP 139, GLU 168, and TYR 201 [102].

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