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NATURAL NANOPARTICLES AID IN THE TREATMENT OF DIABETES AND CANCER: A REVIEW

**GHOSH N, DAS R*, PAL M, KUNDU A, SAHA A, SHARMA C, GHOSH P AND
MOHANTY JP**

Himalayan Pharmacy Institute, Majhitar, East Sikkim-737136

*Corresponding Author: Mr. Rajat Das: E Mail: rajatdas1992@yahoo.com

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ABSTRACT

Nano-technology refers to an emerging field of science that includes synthesis and development of various nanomaterials. Now a days nano-particles are used to treat various chronic and acute diseases such (diabetes, cancer etc). Nanotechnology in diabetes research has facilitated the development of novel glucose measurement and insulin delivery modalities which hold the potential to dramatically improve quality of life for diabetics. The ideal treatment for DM is to find a less expensive anti-diabetic substitute that can work on numerous disease-related targets and pathways. Exciting new opportunities in biological and medication delivery applications have been made possible by nanotechnology. Zinc oxide nanoparticles (ZnO-NPs), one of the emerging nanoparticle agents, have significant implications for treating numerous diseases, including DM. The inherent drawbacks of conventional cancer treatments served as a catalyst for the development and application of various nanotechnologies for safer and more effective cancer treatment, a field referred to as cancer nanomedicine. Despite tremendous technological progress in this area, the complexity and unpredictability of cancer patients tumour biology continue to be the key obstacles to nanomedicine's establishment of a new paradigm in cancer therapy.

Keywords: Nano-technology, Diabetics, Nano-medicine, Cancer, Zinc oxide nanoparticles

INTRODUCTION

Herbal medicine spread all over the world since ancient times, recognized by doctors and patients for better therapeutic value, as they are less harmful than modern medicine. More and more medicinal plants are discovered now a days and getting attention more than ever because they have potential of given great benefits to society, or to everyone. Herbal remedies can help enhance therapeutic value by reducing toxicity and side effects of along with the drug it also increases bioavailability [1]. The main sources of natural compounds are medicinal and aromatic plants, which have been used for centuries in various traditional medical systems around the world to treat or prevent the symptoms of certain diseases [2]. Nanotechnology has received considerable medical attention because nanostructures are more likely to interact with the body at the molecular level. The pharmacokinetics and bio-distribution of active ingredients can be significantly improved by targeting them to designated sites using nano drug delivery systems, thereby increasing efficacy and bioavailability and reducing drug toxicity [3]. It's anticipated that nanotechnology will be used more and more in herbal medicine, specifically in drug delivery. An important component of this strategy is nanotechnology. Future applications for improving

performance and resolving issues with medicinal plant's limitations include nano-herbal drug delivery systems [4]. As a result, serious diseases like cancer and diabetes can be treated with herbal nano-carriers. These organic nano-particles have been engineered in various shapes, sizes and compositions, functionalized and physicochemically modified to achieve specific properties according to the properties of both the drug and the target organ. In addition, inorganic nano-particles such as Nano-particles of alumina, carbon, copper oxide, ceramics, iron oxide, gold, silver, zinc used in phytochemical research [5]. Nanocarriers encapsulating herbal medicines bypass all barriers such as the acidic pH of the stomach and metabolism in the liver to transport optimal amounts of the drug to its site of action and, due to their small size, reduce drug delivery into the blood and increases long-term circulation [6].

The Need for Nano-sized Delivery Systems for Herbal Therapy:

A nano-sized herbal delivery system was chosen to overcome the shortcomings of traditional herbal drug delivery systems for the following reasons.

- Nanoparticles can be used to target herbal medicines to individual organs, improving selectivity, drug delivery,

efficacy and safety, thereby reducing dosage and increasing patient compliance.

- Nanoparticles increase the solubility of herbal medicines and help localize the drug to specific sites, improving potency.
- They appear to be able to deliver high drug concentrations to disease sites due to their unique size and high loading capacity.
- Small particle size drug delivery increases the total surface area of the drug, resulting in faster dissolution into the blood.
- Demonstrates EPR effect (increased permeation and retention). H. Smaller size improves penetration across the barrier and poor lymphatic drainage improves retention. B. intra tumor.
- Demonstrates passive targeting to disease sites of action without the addition of specific ligand moieties.
- Less side effects [7, 8, 9].

Herbal nano particles in cancer therapy

Malignancy, another name for cancer, is the abnormal cell development that results in tumors. Any area of the body can be the source. Cells begin to divide abnormally when their genetic makeup changes. Chemotherapy, radiation, and/or surgery are all used in cancer

treatment. Malignant or cancerous disease is treated with chemotherapy medications, often known as anti-neoplastic drugs. A variety of anticancer medicine classes, including alkylating agents, anti-metabolites, natural products, and hormones, are included in chemotherapeutic medications. In addition to these, there are several medications that may not belong to those classifications but are nonetheless used to treat cancer [10]. The majority of herbal remedies made from plant extracts typically have antioxidant, anti-proliferative, or anti-migratory activity, as well as selectively induced cellular death (apoptosis) and cytotoxic action by using any of the subcellular mechanisms listed below - by lowering the level of lipid peroxidation and acid phosphatase activity, inhibiting the PI3K/Akt pathway, repairing DNA, boosting body immunity, arresting the cell cycle at the G1 stage [11]. Research advances and the creation of advanced technology for extracting active compounds from plants have made it feasible to isolate the primary chemical components responsible for the anticancer effect, each of which has a specific chemical composition and mode of molecular action. The development of formulations and dosage forms for these active substances that address all the drawbacks of the standard dose regimen previously designed for the treatment

of cancer patients, however, presents a subtle but significant obstacle. As a result, several nanoformulations or nanomedicines (polymeric nanoparticles (NPs), dendrimers,

liposomes, nano-tubes, magnetic NPs, gold NPs, etc.) have been produced for anticancer drugs and are in clinical trials [12].

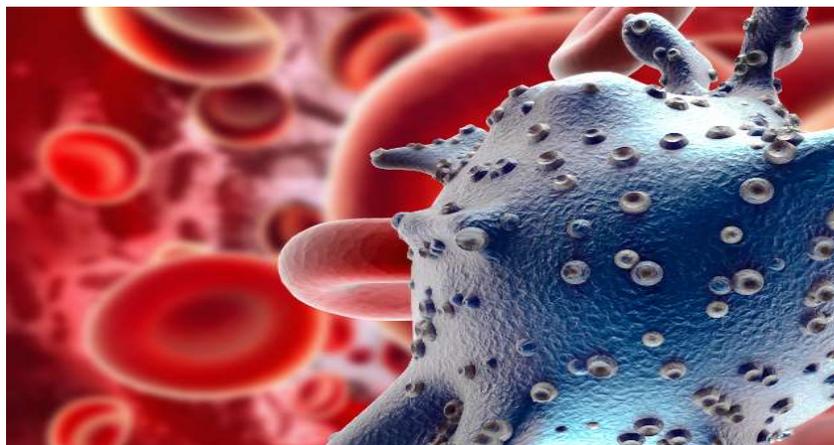


Figure 1: Nanoparticle-treated cancer cells

Literatures on Cancer Therapy:

Journal Name	Major Findings	Ref. No.
Preclinical evaluation of Genexol-PM, a nanoparticle formulation of paclitaxel, as a novel radiosensitizer for the treatment of non-small cell lung cancer.	Genexol-PM, the only clinically approved as a radio sensitizer using non-small cell lung cancer (NSCLC). The amount of paclitaxel administered to healthy liver and lungs after Genexol-PM treatment was measured. Genexol-PM was tested in vitro as a radio sensitizer and shown to be more effective than Taxol, its small molecule analogue, at the half maximal inhibitory concentration. Additionally, they discovered that Genexol-PM causes less paclitaxel exposure to healthy lung tissue than Taxol six hours after treatment	13
Parenterally administrable nano-micelles of 3, 4-difluorobenzylidene curcumin for treating pancreatic cancer.	In contrast to CMN, 3,4-Difluorobenzylidene curcumin (CDF) has enhanced pancreas-specific accumulation in vivo and a longer circulatory half-life while maintaining excellent anticancer activity. Additionally, compared to native CMN, CDF had favourable pharmacokinetic parameters with 10 times larger accumulations in the pancreatic tissue. In the current study, they have developed water-soluble nano-micelles utilising amphiphilic SMA polymer to overcome CDF's solubility problems.	14
Curcumin nanoformulation for cervical cancer treatment.	They present a curcumin nanoparticle formulation (Nano-CUR) based on poly (lactic-co-glycolic acid) to enhance these clinically relevant characteristics. According to this study, Nano-CUR is more effective than free CUR at inhibiting cell growth, inducing apoptosis, and arresting the cell cycle in cervical carcinoma cell lines. Nano-CUR treatment changed variables associated with carcinogenesis, including proteins, transcription factors, and mi-RNAs, and it significantly decreased the malignancy burden in a preliminary study orthotopic mice model.	15
miRNA-205 nanoformulation sensitizes prostate cancer cells to chemotherapy.	An innovative poly(ethyleneimine)-poly(ethylene glycol) layer or layer(s)-based magnetic nanoparticle (MNP)-based nanoplatfrom with an iron oxide core was created. To assess cellular uptake, miR-205 administration, and anticancer, antimetastatic, and chemosensitization potentials against docetaxel therapy, the new formulation was used on prostate cancer cells. These research findings demonstrate a solid proof-of-concept for a unique non-viral nano-particle delivery methodology for efficient micro RNA to prostate cancer cell.	16

Dual-targeted nano-in-nano albumin carriers enhance the efficacy of combined chemo/herbal therapy of lung cancer. Nanomedicine	"Nano-in-Nano" which was used to make it easier to combine the chemotherapy medication berberine (BER) and the antioxidant etoposide (ETP) as a nanosuspension (HSA NPS). For the combined delivery of etoposide (ETP) and berberine (BER) for systemic therapy of lung cancer, this work focused on the formulation of dual tumor-targeted human serum albumin nanoparticles (HSA NPS). Various cross linkers could be used to achieve the sustained release of the water-soluble herbal medicine BER from HSA NPs.	17
Decorating protein nanospheres with lactoferrin enhances oral COX-2 inhibitor/herbal therapy of hepatocellular carcinoma.	They created hydrophobic gliadin nanoparticles (GL-NPs) for the targeted distribution of celecoxib (CXB) and diosmin by using the nano-precipitation process and spray-drying (DSN). The surface of the drug-loaded GL-NPs was coated with lactoferrin (LF) via electrostatic interactions for binding to the asialoglycoprotein receptors over expressed by human liver malignant cells in order to accomplish active tumor-targeting.	18
Lactoferrin-tagged quantum dots-based theranostic nanocapsules for combined COX-2 inhibitor/herbal therapy of breast cancer.	Multifunctional nano theranostics using lactoferrin/chondroitin layer-by-layer constructed nanocapsules (NCs) and highly fluorescent quantum dots (QDs) for systemic delivery of the breast cancer treatments celecoxib (CXB) and honokiol (HNK). By utilizing their capacity to guarantee nanocarrier internalization via OFF-ON state shifting, our nanoplatforms could be used as a theranostic tool in the therapeutic and cancer imaging fields. Natural biodegradable polymers were used to surface-functionalize NCs in order to aggressively target cancer cells through over expressed LF and CD44 receptors.	19
Tumor-targeting delivery of herb-based drugs with cell-penetrating/tumor-targeting peptide-modified nanocarriers.	The creation of novel forms of CPP was prompted by their lack of specificity and in vivo degradation. Currently, nanocarriers enhanced with activable CPP and tumor-targeting peptide (TTP) have significantly better cellular selective uptake, cytotoxicity, and tumor growth suppression. They highlight recent developments in CPP-based tumor-targeting techniques as well as their limitations in tumor delivery systems in this study. Finally, we discuss the use of CPPs and TTPs in the delivery of chemotherapeutic drugs derived from plants.	20
Next-generation paclitaxel-nanoparticle formulation for pancreatic cancer treatment.	The GEN-solid lipid nano-particles (SLNs) were made using the solvent injection method, and the TRE/zein layer coating the SLN core was added using the nano-precipitation method. The hydrophobic ion pairing between TRE and stearyl amine improved the integration of TRE in MLPN and the stability of nanoparticles due to the negative charge on TRE. The EPR effect and cellular internalization of MLPNs into cells were both facilitated by the tiny particle size of MLPNs, which also boosted the accumulation of nanoparticles inside tumor tissue	21
Nanomedicine: Nanotechnology, Biology and Medicine	A multi-layered poly (lactic-co-glycolic acid) nanoparticle formulation (PPNPs) that is stabilised by Pluronic F127 and polyvinyl alcohol and coated with poly-L-lysine and loaded with the drug paclitaxel was studied. Reduced expression of tumour-related and metastasis-related proteins (ki67,vimentin, and slug) was seen in mice treated with PPNPs in immune histochemistry of orthotopic tumors. These findings imply that PPNPs serve as a solid and workable basis for pancreatic cancer.	22

Herbal nano particles in diabetics treatment

Despite the great scientific advancements of the past century, diabetes continues to be a serious health problem worldwide, causing millions of deaths every year and severely limiting the lives of many people with its life-

threatening complications [23]. Sadly, the available medications, including metformin, the first-line treatment for diabetes, can only postpone the onset of the condition. Other negative effects experienced by people using these medications include lactic acidosis, obesity, and liver damage [24, 25]. To control

the disease, it is often necessary to combine numerous therapy regimens because many individuals develop tolerance to the therapies after they begin [26]. Smart nanostructures and nanotechnology have recently demonstrated significant promise for a wide range of biomedical applications, including monitoring, diagnosing, repairing, and treating human biological systems. Compared to conventional nano-medicines, nanoscale metal-organic frameworks (NMOFs), made from the self-assembly of polydentate bridging ligands and metal-connecting points,

have various advantages, including their inherent biodegradability and structural and chemical variation [27, 28]. As a result, it was discovered that using nano-particles could be a viable strategy for overcoming the challenges associated with the use of herbal medications [29]. Due to their unique qualities, such as their small dimensions, capacity to carry drugs through cell membranes, and bio-adaptability, nano-materials have recently gained attention for use in antidiabetic studies [30, 31].



Figure 2: Nanotechnology to monitor blood glucose level

Literatures on Diabetic therapy:

Journal Name	Major Findings	Ref. No.
Development of stevioside Pluronic-F-68 copolymer based PLA-nanoparticles as an antidiabetic nanomedicine	stevioside (an FDA-approved nontoxic natural non-caloric sweetener) has been shown to have excellent anti-diabetic potentia. To improve bioavailability and overcome poor intestinal absorption, we nano-bioconjugated this molecule to biodegradable Pluronic-F-68 copolymer-based PLA nanoparticles using the nanoprecipitation method (spherical, size range 110-130 nm). This newly developed nanostevioside has an extremely high potential for application as an antidiabetic nanomedicine for secure and effective.	32
gymnemic acids nanoparticulate formulations against diabetes mellitus	Gymnemic acid nanoparticulate formulations investigated for anti-diabetic activity have produced notable reductions in blood glucose and other issues related to diabetes. The nano-formulations significantly reduced blood sugar levels and had anti-hyperglycemic effects. Compared to the commercially available gymnemic acid tablets, the outcomes are significantly superior. The study unequivocally demonstrates that the proposed gymnemic acid nanoparticulate formulations may be a better therapeutic adjuvant choice for persons with diabetes mellitus.	33

A newly developed silymarin nanoformulation as a potential antidiabetic agent in experimental diabetes	silymarin (SM) nanoformulation that is stable, biocompatible, and safe is being developed as part of the study. The nano-precipitation process was adapted to load SM into pluronic nano micelles (SMnp). Utilizing streptozotocin (STZ)-induced diabetic rats under identical experimental settings, the study offers the first side-by-side evaluation of SMnp and its native form (SM) as antidiabetic drugs. Comparing the newly developed SMnp to the native candidate SM utilizing STZ-induced diabetes in rats, the newly developed SMnp's antihyperglycemic characteristics were assessed.	34
S.Bioextract-mediated ZnO nanoparticles: microwave-assisted synthesis, characterization and antidiabetic activity evaluation	Vaccinium Arctostaphylos L, fruit extract, ZnO nanoparticles were produced utilizing the microwave-assisted technique. By using XRD, SEM, TEM, EDX, FT-IR, UV-vis DRS, and TGA analysis, the materials structure, size, morphology, and optical characteristics were identified. The alloxan-induced diabetes rats were split into groups that were not treated (diabetic control group) and those that did get insulin, chemically synthesized ZnO, plant extract, and biologically synthesized ZnO along with a normal, healthy control group. Immediately following therapy, fasting blood sugar (FBS), high-density lipoprotein (HDL), total triglyceride (TG), total cholesterol (TC), and insulin levels were measured.	35
Exploiting antidiabetic activity of silver nanoparticles synthesized using Punica granatum leaves and anticancer potential against human liver cancer cells	The unique synthesis of silver nanoparticles (AgNPs) utilizing a Punica granatum leaf extract is described in this paper for the first time (PGE). AgNPs that had been produced were examined for composition and oxidation state using an XPS surface-sensitive method. The α -amylase and α -glucosidase activities of PGE-AgNPs were effectively inhibited. Human liver cancer cells (HepG2) responded to the PGE-AgNPs in a dose-dependent manner, showing that it is more effective at eliminating cancer cells.	36
Cladosporium species-mediated synthesis of silver nanoparticles possessing in vitro antioxidant, anti-diabetic and anti-Alzheimer activity	This study looked at the effects of antioxidant, anti-diabetic, anti-acetylcholinesterase (AChE), and anti-butyrylcholinesterase (BChE) activities on the synthesis of AgNPs utilizing an aqueous extract of endophytic fungi, Cladosporium species (CsAgNPs). Silver nanoparticles produced by Cladosporium species were examined using a UV-Vis spectrophotometer, FTIR, X-ray diffraction (XRD), and energy-dispersive X-ray spectroscopy (EDX). The aqueous extract of Cladosporium species has been found to include phenolic glycosides, terpenoids, alkaloids, phenol, and anthraquinones in addition to carbohydrates and tannin.	37
Nanotechnological approaches for the development of herbal drugs in treatment of diabetes mellitus	Due to their efficiency, lack of negative side effects, and affordable price, herbal medications are frequently given. Up-to-date, nanoformulation of herbal medications was included in the available literature on folkloric medicine used to treat diabetes. Recent research has demonstrated the potential of nanotechnology for use in a variety of biological and medical applications, particularly as targeted drug delivery systems to lessen and postpone the chronic consequences of diabetes.	38
A novel pharmacological approach of herbal mediated cerium oxide and silver nanoparticles with improved biomedical activity in comparison with Lawsonia inermis	A promising idea for the treatment of diabetes is the use of nanoparticles as a medication. In the current investigation, the in-vivo hypoglycemic effects of herbal-mediated cerium oxide nanoparticles (HMCeO ₂ NPs), herbal-mediated silver nanoparticles (HMAg NPs), and Lawsonia inermis extract (LIE) were assessed, and their potencies were compared. The resulting HMCeO ₂ NPs, HMAg NPs, and Lawsonia inermis have all been characterized using various analytical tools. Following the recommendations of OECD-425, the acute oral toxicity of the synthesized NPs and Lawsonia inermis extract was evaluated using a female albino mouse model.	39
Nano-suspension of ursolic acid for improving oral bioavailability and attenuation of type II diabetes	The goal of the current work is to create ursolic acid nanoparticles that will increase their bioavailability and then be tested for their antidiabetic effectiveness. Ursolic acid nanoparticles were created using the nanoprecipitation method, and their production was optimised by adjusting the PVA concentration in the formulation and the stirring speed in the processing. By monitoring blood glucose level, in vivo antidiabetic impact was calculated. Ursolic acid nanoparticle significantly ($p < 0.001$) decreased the high blood glucose level in a dose-dependent manner with a substantial lipid-lowering and antioxidant effect.	40

<p>Effect of co-administration of herbal extracts with copper nanoparticles: a novel two-pronged approach in treating type 2 diabetes</p>	<p>The goal of the study is to determine how administration of cremated copper nanoparticle alone, polyherbal extracts of four herbs alone, and the combination of incinerated copper nanoparticles-polyherbal extracts affect streptozotocin-induced type 2 diabetic mice. Compared to the animals in the groups that received a combined therapy, the reaction was shown to be much weaker in the case of the rats given either the extracts alone or the nanoparticles alone. The study's findings made it abundantly evident that administering copper nanoparticles and polyherbal extracts together, as opposed to administering just copper nanoparticles or just polyherbal extracts, had a protective effect on the body.</p>	<p>41</p>
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Future Prospects & Recommendation:

Compared to many previous innovations, nanotechnology will have a more significant impact on dentistry, healthcare, and human existence. The greatest wish of every doctor in the world will at last come true once nano-mechanics are available. Dental professionals and medical professionals will be able to perform curative and reconstructive surgeries at the cellular and molecular levels thanks to programmable and controlled micro scale robots made of nanoscale parts built with nanometer precision. They must first adhere to all safety regulations before that. The materials that are currently accessible from nanotechnology through green nanotechnology have better properties than their prior ones and have complied with safety standards. So instead of waiting for Nanotechnology has developed into the basis for astounding industrial applications and exponential growth in a period of around 50 years. For instance, nanotechnology has had a significant influence on medical equipment including imaging probes, drug delivery

systems, and diagnostic biosensors in the pharmaceutical communities of practise. The usage of nano-materials has significantly risen in the food and cosmetics sectors for enhancements in manufacturing, packaging, shelf life, and bioavailability. In order to determine the quality and safety of food, nano-particles are currently utilised as food sensors. Zinc oxide quantum dot nano-particles have antibacterial activity against bacteria that are found in food. Things to happen, let's start believing and do our part to make you healthier. Nanotechnology now has an everyday influence on human existence. There are numerous and varied possible advantages. However, there is serious worry about the possible health and environmental concerns due to the vast human exposure to nanoparticles. These worries sparked the development of new scientific fields including nano-toxicology and nano-medicine. The study of nano-particles possible harmful effects on human health is known as nano-toxicology. To investigate the advantages and dangers of using nanoparticles in medicine

and medical devices, the field of nanomedicine was created. This field comprises subfields including tissue engineering, biomaterials, biosensors, and bio-imaging. Improved medication delivery, antimicrobial coatings for medical equipment, less inflammation, faster surgical tissue repair, and the identification of circulating cancer cells are just a few of the potential advantages of medical nanomaterials. However, given the dearth of trustworthy toxicology data, the potential to affect human health continues to be a major concern.

REFERENCES

- [1] Kesarwani K, Gupta R. Bioavailability enhancers of herbal origin: An overview. *Asian Pacific journal of tropical biomedicine*. 2013 Apr 1;3(4):253-66.
- [2] Ahmed HM. Ethnopharmacobotanical study on the medicinal plants used by herbalists in Sulaymaniyah Province, Kurdistan, Iraq. *Journal of ethnobiology and ethnomedicine*. 2016 Dec;12(1):1-7.
- [3] De Oliveira RO, de Santa Maria LC, Barratt G. Nanomedicine and its applications to the treatment of prostate cancer. *In Annales pharmaceutiques francaises* 2014 Sep 1 (Vol. 72, No. 5, pp. 303-316). Elsevier Masson.
- [4] Goyal A, Kumar S, Nagpal M, Singh I, Arora S. Potential of novel drug delivery systems for herbal drugs. *Indian journal of pharmaceutical education and research*. 2011 Jul 1;45(3):225-35.
- [5] Sarker SD, Nahar L. Application of nanotechnology in phytochemical research. *Pharmaceutical Sciences*. 2017 Sep 23;23(3):170-1.
- [6] Thapa RK, Khan GM, Parajuli-Baral K, Thapa P. Herbal Medicine Incorporated nanoparticles: Advancements in herbal treatment. *Asian journal of biomedical and pharmaceutical sciences*. 2013;3(24).
- [7] Ansari SH, Islam F, Sameem M. Influence of nanotechnology on herbal drugs: A Review. *Journal of advanced pharmaceutical technology & research*. 2012 Jul;3(3):142.
- [8] Sharma M. Applications of nanotechnology based dosage forms for delivery of herbal drugs. *Research and Reviews: Journal of pharmaceutics and nanotechnology*. 2014 Jan;2(1):456.
- [9] Chidambaram M, Manavalan R, Kathiresan K. Nanotherapeutics to overcome conventional cancer chemotherapy limitations. *Journal of*

- pharmacy & pharmaceutical sciences. 2011 Feb 16;14(1):67-77.
- [10] Rahman M, Ahmad MZ, Kazmi I, Akhter S, Afzal M, Gupta G, Jalees Ahmed F, Anwar F. Advancement in multifunctional nanoparticles for the effective treatment of cancer. *Expert Opinion on Drug Delivery*. 2012 Apr 1;9(4):367-81.
- [11] Sakarkar DM, Deshmukh VN. Ethnopharmacological review of traditional medicinal plants for anticancer activity. *Int J Pharm Tech Res*. 2011 Jan;3(1):298-308.
- [12] Ud Din F, Aman W, Ullah I, Qureshi OS, Mustapha O, Shafique S, Zeb A. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. *International journal of nanomedicine*. 2017;12:7291.
- [13] Werner ME, Cummings ND, Sethi M, Wang EC, Sukumar R, Moore DT, Wang AZ. Preclinical evaluation of Genexol-PM, a nanoparticle formulation of paclitaxel, as a novel radiosensitizer for the treatment of non-small cell lung cancer. *International Journal of Radiation Oncology* Biology* Physics*. 2013 Jul 1;86(3):463-8.
- [14] kesharwani P, Banerjee S, Padhye S, Sarkar FH, Iyer AK. Parenterally administrable nano-micelles of 3, 4-difluorobenzylidene curcumin for treating pancreatic cancer. *Colloids and Surfaces B: Biointerfaces*. 2015 Aug 1;132:138-45.
- [15] Zaman MS, Chauhan N, Yallapu MM, Gara RK, Maher DM, Kumari S, Sikander M, Khan S, Zafar N, Jaggi M, Chauhan SC. Curcumin nanoformulation for cervical cancer treatment. *Scientific reports*. 2016 Feb 3;6(1):20051.
- [16] Nagesh PK, Chowdhury P, Hatami E, Boya VK, Kashyap VK, Khan S, Hafeez BB, Chauhan SC, Jaggi M, Yallapu MM. miRNA-205 nanoformulation sensitizes prostate cancer cells to chemotherapy. *Cancers*. 2018 Aug 25;10(9):289.
- [17] Elgohary MM, Helmy MW, Mortada SM, Elzoghby AO. Dual-targeted nano-in-nano albumin carriers enhance the efficacy of combined chemo/herbal therapy of lung cancer. *Nanomedicine*. 2018 Sep;13(17):2221-4.
- [18] Abdelmoneem MA, Mahmoud M, Zaky A, Helmy MW, Sallam M, Fang JY, Elkhodairy KA, Elzoghby

- AO. Decorating protein nanospheres with lactoferrin enhances oral COX-2 inhibitor/herbal therapy of hepatocellular carcinoma. *Nanomedicine*. 2018 Oct;13(19):2377-95.
- [19] Abdelhamid AS, Zayed DG, Helmy MW, Ebrahim SM, Bahey-El-Din M, Zein-El-Dein EA, El-Gizawy SA, Elzoghby AO. Lactoferrin-tagged quantum dots-based theranostic nanocapsules for combined COX-2 inhibitor/herbal therapy of breast cancer. *Nanomedicine*. 2018 Oct;13(20):2637-56.
- [20] Kebebe D, Liu Y, Wu Y, Vilakhamxay M, Liu Z, Li J. Tumor-targeting delivery of herb-based drugs with cell-penetrating/tumor-targeting peptide-modified nanocarriers. *International journal of nanomedicine*. 2018;13:1425.
- [21] Kamel NM, Helmy MW, Samaha MW, Ragab D, Elzoghby AO. Multi-compartmental lipid-protein nanohybrids for combined tretinoin/herbal lung cancer therapy. *Nanomedicine*. 2019 Sep;14(18):2461-79.
- [22] Massey AE, Sikander M, Chauhan N, Kumari S, Setua S, Shetty AB, Mandil H, Kashyap VK, Khan S, Jaggi M, Yallapu MM. Next-generation paclitaxel-nanoparticle formulation for pancreatic cancer treatment. *Nanomedicine: Nanotechnology, Biology and Medicine*. 2019 Aug 1;20:102027.
- [23] <https://www.idf.org> [homepage on the Internet] Strategic Implementation Plan. International Diabetes Federation; 2016. [Accessed March 20, 2016].
- [24] Rojas LB, Gomes MB. Metformin: an old but still the best treatment for type 2 diabetes. *Diabetology & metabolic syndrome*. 2013 Dec;5(1):1-5.
- [25] Raz I, Eldor R. Rational therapy for diabetes: early recognition of adverse effects and avoidance of disruptive false alarms. *Diabetes/metabolism research and reviews*. 2012 May;28(4):321-4.
- [26] Chen ZC, Zhang SL, Yan L, Wu MC, Chen LH, Ji LN. Association between side effects of oral anti-diabetic drugs and self-reported mental health and quality of life among patients with type 2 diabetes. *Zhonghua yi xue za zhi*. 2011 Jan 1;91(4):229-33.

- [27] Dincă M, Long JR. Hydrogen storage in microporous metal–organic frameworks with exposed metal sites. *Angewandte Chemie International Edition*. 2008 Aug 25;47(36):6766-79.
- [28] Rowsell JL, Yaghi OM. Strategies for hydrogen storage in metal–organic frameworks. *Angewandte Chemie International Edition*. 2005 Jul 25;44(30):4670-9.
- [29] Thapa RK, Khan GM, Parajuli-Baral K, Thapa P. Herbal Medicine Incorporated nanoparticles: Advancements in herbal treatment. *Asian journal of biomedical and pharmaceutical sciences*. 2013;3(24).
- [30] Karthick V, Kumar VG, Dhas TS, Singaravelu G, Sadiq AM, Govindaraju K. Effect of biologically synthesized gold nanoparticles on alloxan-induced diabetic rats—an in vivo approach. *Colloids and Surfaces B: Biointerfaces*. 2014 Oct 1;122:505-11.
- [31] Sharma R, Gupta U, Garg NK, Tyagi RK, Jain NK. Surface engineered and ligand anchored nanobioconjugate: an effective therapeutic approach for oral insulin delivery in experimental diabetic rats. *Colloids and Surfaces B: Biointerfaces*. 2015 Mar 1;127:172-81.
- [32] Barwal I, Sood A, Sharma M, Singh B, Yadav SC. Development of stevioside Pluronic-F-68 copolymer based PLA-nanoparticles as an antidiabetic nanomedicine. *Colloids and Surfaces B: Biointerfaces*. 2013 Jan 1;101:510-6.
- [33] Ravichandran R. Studies on gymnemic acids nanoparticulate formulations against diabetes mellitus. *International Journal of Biomedical and Clinical Engineering (IJBCE)*. 2012 Jul 1;1(2):1-2.
- [34] El-Far YM, Zakaria MM, Gabr MM, El Gayar AM, El-Sherbiny IM, Eissa LA. A newly developed silymarin nanoformulation as a potential antidiabetic agent in experimental diabetes. *Nanomedicine*. 2016 Oct;11(19):2581-602.
- [35] Bayrami A, Parvinroo S, Habibi-Yangjeh A, Rahim Pouran S. Bio-extract-mediated zno nanoparticles: microwave-assisted synthesis, characterization and antidiabetic activity evaluation. *Artificial cells, nanomedicine, and biotechnology*. 2018 May 19;46(4):730-9.

- [36] Rijuta G. Saratalea, Han Seung Shinb, Gopalakrishnan Kumarc, Giovanni Benellid, Dong-Su Kime and Ganesh D. Sarataleb, Exploiting antidiabetic activity of silver nanoparticles synthesized using *Punica granatum* leaves and anticancer potential against human liver cancer cells (hepg2), 2018 VOL. 46, NO. 1, 211–222.
- [37] Popli D, Anil V, Subramanyam AB, MN N, VR R, Rao SN, Rai RV, Govindappa M. Endophyte fungi, *Cladosporium* species-mediated synthesis of silver nanoparticles possessing in vitro antioxidant, anti-diabetic and anti-Alzheimer activity. *Artificial cells, nanomedicine, and biotechnology*. 2018 Oct 31;46(sup1):676-83.
- [38] Saritha Marella, Naga Venkata Krishna Vara Prasad Tollamadugu, Nanotechnological approaches for the development of herbal drugs in treatment of diabetes mellitus – a critical review, 2018, Vol. 12 Iss. 5, pp. 549-556.
- [39] Kalakotla S, Jayarambabu N, Mohan GK, Mydin RB, Gupta VR. A novel pharmacological approach of herbal mediated cerium oxide and silver nanoparticles with improved biomedical activity in comparison with *Lawsonia inermis*. *Colloids and Surfaces B: Biointerfaces*. 2019 Feb 1;174:199-206.
- [40] Singh AK, Pandey H, Ramteke PW, Mishra SB. Nano-suspension of ursolic acid for improving oral bioavailability and attenuation of type II diabetes: A histopathological investigation. *Biocatalysis and Agricultural Biotechnology*. 2019 Nov 1; 22: 101433.
- [41] Singh S, Singh SK, Kumar B, Kaur B, Khursheed R, Gulati M, Pandey NK, Prabhakar PK, Baghel DS, Porwal O, Awasthi A. Effect of co-administration of herbal extracts with copper nanoparticles: a novel two-pronged approach in treating type 2 diabetes. *Recent Innovations in Chemical Engineering (Formerly Recent Patents on Chemical Engineering)*. 2020 Nov 1;13(5):366-78.