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Bifunctional Antidiabetic - Anticancer Active Vitamins and Minerals: Drug Delivery Systems Enhancement

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Abstract

Vitamins and minerals are essential micronutrients required for normal development and function of human body They are known to be deficient in chronic illness like diabetes mellitus and cancer.

Bifunctional antidiabetic and anticancer vitamins and minerals have effective dual functions and roles in the management of diabetes and cancer. This is due to their unique ability to interact and interfere in the pathways implicated in both diseases.

Examples of these bifunctional anticancer-antidiabetic vitamins and minerals include:

1. Vitamins: vitamin A, B, C, D, E and K

2. Minerals and trace elements: Zinc, Selenium, Manganese and vanadium.

These agents are active alone or when combined with conventional therapeutic drugs.

Drug delivery systems are methods that assist the regulated delivery of pharmaceutical agents to the body by enhancing their pharmacokinetic properties and improving their bioavailability, using mainly nanotechnology principles. Examples of these nanoparticles include chitosan, alginate, solid lipid nanoparticles and liposomes.

The aim of this review is to describe the roles of these bifunctional antidiabetic-anticancer vitamins and minerals in the management of both diseases. And also, to highlight the importance of the various drug delivery systems in greatly enhancing the therapeutic efficacy of these bifunctional vitamins and minerals.

Introduction

Several vitamins and minerals are known to have antidiabetic and anticancer dual roles.

This is because oxidative stress appears to be a common underlying pathology to both disease [1, 2]. As such, vitamins and minerals have key roles to play in the management of both diseases especially when concurrent.

Diabetic patients are known to be deficient in certain vitamins, like subcomponents of Vitamin B complex which plays key role in peripheral neuropathy. There are renewed interests in Vitamin C (high dose intravenous therapy) in combatting advanced and resistant cancers due to its potent cytotoxic effect that is not unconnected to its antioxidant properties [3]. Vitamin D deficiency is known to play a role in onset of diabetes [4]. Low level of vitamin D is linked to aggressive prostate cancer [5, 6].

The use of Antioxidants and supplements in cancer treatment is controversial and discouraged by some schools of thought due to the ability of these drugs to reduce the effectiveness of chemotherapy and radiotherapy and interact with treatment drugs [7, 8]. That notwithstanding, these properties are also known to have beneficial effects on normal cells by reducing the side effects of chemotherapy and radiotherapy on normal tissues [9].

Examples of vitamins and minerals that have dual anticancer and antidiabetic effects include:

1) Vitamins: vitamin A, B (B3), C, D (D3), E (Tocopherols and Tocotrienols) and K (K3 mainly, also K1 and K2).

2) Minerals: Zinc, Selenium, Manganese and vanadium.

The role of drug delivery systems in the management of cancer and diabetes can never be overemphasized. These include drug vehicles, diagnostic, theranostic, therapeutic and targeted therapy. There are lots of advances and expansion in biotechnology and nanoparticles - based therapeutics. Majority of these are proteins and peptides. Cell and gene therapies are very advanced means of drug delivery therapeutics [10].

This review aims to highlight the roles of these bifunctional vitamins and minerals in the management of diabetic patients with concurrent cancer illness or cancer patients with glucose intolerance. These drugs (especially the minerals and trace elements) can be used as complex forming agents and nanoparticles, and

can equally be complexed to other nanoparticles and drug delivery systems to markedly increase their utility as bifunctional anticancer-antidiabetic agents.

Efficient drug delivery systems will markedly increase their effectiveness by improving their stability, obviating the biological interferences in vivo to increase their bioavailability and duration of action [11].

Dual – Acting Vitamins with Antidiabetic- Anticancer Properties

1. Vitamin A: regular intake of dietary vitamin A and carotenoids reduces the risk of squamous cell carcinoma [12]. Retinol and Vitamin A derivatives play important role in cell differentiation, proliferation and apoptosis. The bioavailability of retinoid inside cells is controlled the presence of cytoplasmic retinol and retinoic acid binding proteins (CRBPs and CRABPs). CRBP-1 is important in wound healing and remodeling of arterial tissues. Downregulation of CRBP-1 is linked with aggressive phenotypes in breast, ovarian and nasopharyngeal cancers, while re-expression of CRBP – 1 increase sensitivity to retinol and decrease the viability of ovarian cancer cells [13].

Development of Diabetes is linked to changes in vitamin A metabolism [14]. Vitamin A supplementation has important role in type 2 diabetes [15]. Retinoic acid a metabolite of vitamin A through its receptors Retinoic acid receptors (RARs) and retinoid X receptors (RXRs) that are transcription factors interact and synergize with insulin to regulate the expression of genes in hepatic glucose and lipid metabolism [16].

2. Vitamin B (B3): A phase 3, double-blind, randomized controlled trial In Sydney Australia showed that oral nicotinamide was safe and effective in decreasing the incidence of nonmelanoma skin cancers and actinic keratoses [17]. Epidemiologic study in US showed beneficial role of niacin intake against Squamous Cell Carcinoma [18]. Researchers using bioluminescent imaging however discovered that nicotinamide riboside at high dose increases risk of triple negative breast cancer and chances of metastases to brain [19].

Alloxan induced diabetic rats when treated with niacin supplementation recovered in almost all measured parameters in a dose dependent relationship. Very noticeable was a reduction in oxidative stress and fasting glucose level parameters [20]. Though a known cause of hyperglycemia, nicotinamide has been found to lower glucose level and prevent peripheral nerve damage in prediabetic and type 2 diabetic mice [21].

3. Vitamin C: Vitamin C was first discovered to have anticancer effects in the 1930s. Its anticancer activities in KRAS or BRAF mutated cells has been linked to dehydroascorbate (DHA) vitamin C oxidized form. Vitamin C is transported into cells through sodium cotransporters but DHA is competitively taken into cells through glucose transporters (GLUT 1 and 4) before being reduced back to vitamin C [22]. Vitamin C is known to induce apoptosis in drug-resistant tumor cells and regulate tumor cells growth and metastases. It equally regulated JAK-STAT, TGF/SMAD, TRAIL and microRNAs in various tumors [23].

At a dose of 1000mg, vitamin C significantly reduces the fasting blood sugar (FBS), triglyceride (TG), low density lipoprotein (LDL), HbA1c and serum insulin in a research group while dose of 500mg did not cause significant change in these parameters [24]. Systematic Review and Meta-analysis of Randomized Controlled Trials concluded that short-term studies showed that Vitamin C enhances glucose control and blood pressure in patients with type 2 diabetes [25].

4. Vitamin D (D3): Ecological researches of cancer linked to data from solar radiation showed that Vitamin D reduces risks of incidence and mortality for 23 different cancers. Observational studies meta-analysis showed inverse relationship between serum 25-hydroxyvitamin D and incidence of 12 different cancers [26]. Even though various analogs of calcitriol (1α, 25(OH)2D3) demonstrated power anticancer effects on cell cultures, a supraphysiological dose is needed in vivo and this can lead to calcemic side effects like hypercalcemia and hypercalciuria [27].

25-hydroxyvitamin D level is inversely linked to insulin resistance [28]. Vitamin D deficiency is linked with insulin resistance in nondiabetics and also linked to decreased insulin formation in type 2 diabetics [29].

5. Vitamin E: Has 8 isoforms Tocopherol α, β, δ, ϒ and Tocotrienol α, β, δ, ϒ. In vitro studies showed anticancer effects with non- alpha tocopherol isoforms of vitamin E [30]. In vitro research with Vitamin E compounds and novel vitamin E-based analogues showed proapoptotic properties like regenerating of apoptotic signaling tracts and inhibition of prosurvival signaling pathways [31].

Vit E supplementation contribute in delaying onset of diabetic complications and slows down its progression [32]. It was also found to reduce the risk of developing cardiovascular diseases in Hp 2-2 diabetic genotype [33]. Systematic review of 9 trials involving 418 patients showed that vitamin E supplementation reduces HbA(1c) in patients with poor glycemic control or low serum concentration of vitamin E, but no beneficial effect in type 2 diabetes mellitus with well controlled glucose level [34].

6. Vitamin K (K1, K2, K3, K4, K5): Vitamin k analogs when combined with chemotherapeutic drugs improved efficacy of chemotherapeutics by enhancing apoptosis and cell cycle arrest and overcome drug resistance by blocking P-glycoprotein [35]. Vitamin K2 was found to activate differentiation and apoptosis in various tumor cell lines, while vitamin k3 and its analogues (naphthoquinone; menadione) showed potent anticancer activities against TK10 renal, UACC62 melanoma, MCF7 breast, HELa cervical, PC3 prostate and HepG2 liver cancer cell lines [36, 37].

Vitamin k2 enhanced insulin sensitivity through the vitamin K – dependent – protein osteocalcin. Vitamin K2 showed superior effects than vitamin K1 on type 2 Diabetes mellitus [38]. Systematic review of the role of various forms of vitamin K on

diabetes and pre-diabetes showed significant decrease in blood glucose (6 studies), increased fasting serum insulin (4 studies), decreased HbA1c (3 studies) [39].

Dual – Acting Minerals with Antidiabetic- Anticancer Properties

1. Zinc: Many epidemiological researches have shown link between zinc deficiencies and the risk of cancer. Unfortunately, zinc reserves are not stored in humans [40]. Zinc was found to be deficient in 65% of patients with head and neck cancers and this severely affected the Natural killer cell activity and IL-2 generation. The cellular zinc level was more prognostic than the nutritional status of the tumor burden and disease stage in these patients as tit correlated more with the frequency of admissions and incidences of infections [41, 42].

Zinc treatment enhances carbohydrate and lipid metabolism diabetic rodent models. It facilitates glucose transport and lipid production and blocks gluconeogenesis and lipolysis [43]. A systemic review and meta-analysis of researches on the outcome of zinc supplementation in diabetes showed significant reduction of blood glucose, lipid parameters, diastolic and systolic blood pressures in zinc treated group [44].

2. Selenium: Redox active selenium compounds have important application in chemotherapy [45]. Other selenium anticancer mechanism include: antioxidant protection, promotion of carcinogen detoxification, promotion of immune surveillance, regulation of cell growth, inhibition of cancer invasion and angiogenesis [46]. The various classes of Selenium-containing compounds involved in chemoprevention include inorganic (selenite, selenate), organic (diselenides, selenides, selenoesters, methylseleninic acid) selenoamino acids and Selol [47].

Reduction in fasting blood glucose, HbA1c, insulin and leptin and improved glucose metabolism were observed when diabetic mice model when treated with Selenium-enriched Bifidobacterium longum DD98 (Se-B. longum DD98), B. longum DD98 or sodium selenite (Na2SeO3). Studies on serum selenium and diabetes in U.S. Adults concluded that in a probability sample of U.S. population, high serum selenium levels were positively associated with the prevalence of diabetes [48]. However, a systematic review and meta-analysis to investigate any link between Selenium and type 2 diabetes concluded that consistent moderate associations exist only between high levels of dietary or serum selenium and prevalent type 2 diabetes and inconsistent results among studies aimed at assessing incident type 2 diabetes; and no consistent evidence that selenium supplementation plays a role in type 2 diabetes development among adults [49].

3. Manganese (Mn): Mn-insufficient mice had very much increased tumor growth and metastasis, with significantly decreased tumor-infiltrating CD8+ T cells. Mn2+ enhances Dendritic cells and macrophage maturation and tumor-specific antigen presentation, enhanced CD8+ T cell differentiation, activation and NK cells activation and increased memory CD8+ T cells [50]. Mn inhibited viability of prostate cancer cell lines through arrest at G0/G 1, and induction of apoptosis, with the effect and intracellular concentrations greatest for PC3 followed by LNCaP, then DU145 cells [51]. A systematic review and meta-analysis to investigate the relationship between Mn levels and Hepatocellular carcinoma (HCC) showed dietary intake of Mn was inversely related with HCC. Also, Mn levels in HCC were very much less than in healthy controls. In tissues, Mn levels in tumors were very much lower than in nearby normal tissues [52].

Several studies have shown manganese deficiency to be common in type 2 diabetes and that Mn supplementation increases insulin sensitivity and regulate glucose. Manganese deficiency is equally linked to insulin resistance similar to type 2 diabetes [53-56]. Two prospective cohort studies in China showed that dietary Mn is inversely linked to type 2 diabetes [57].

4. Trientine (TETA): Triethylenetetramine is a copper chelating agent, included in this review due to its important in the management of Wilson's disease and its usefulness as an anticancer agent. This is due to the role copper plays in tumor proliferation by enabling tumor cells to escape growth inhibitors and avoid death. Trientine enhance chemoprophylaxis against rat liver carcinogenesis through inhibition of angiogenesis [58]. Trientine showed a more potent inhibitory properties than penicillamine (another copper chelator) against murine HCC xenograft model through inhibition of angiogenesis and promotion of apoptosis. Combination of both penicillamine and trientine showed synergistic effect [59].

Copper plays a key role in oxidative stress and pathogenesis of type 2 Diabetes Mellitus and also in the worsening of the disease.
Reactive oxygen species (ROS) are induced under diabetic conditions and are linked in the etiopathogenesis of the disease. Reactive oxygen formation is enhanced by the presence of copper ion through the Fenton reaction. Both copper ion and ROS levels were very much higher in diabetic C57BL/KsJ-db/db Mice compared to the nondiabetic mice. The treatment with copper chelating agent reduced insulin resistance and improved glucose tolerance in diabetic db/db mice [60]. Meta analysis and systematic review of copper levels in type 1 and type 2 diabetes mellitus showed higher concentration of copper in diabetic patients than healthy individuals [61].

5. Vanadium: this trace element with insulin-mimetic features has found usefulness as a nanoparticle in complexing with other agents in the management of either diabetes or cancer.
It interacts with many enzymes involved oncogenes as tumor markers or catalyst namely phosphatases, ATPases, peroxidases, ribonucleases, protein kinases and oxidoreductases. It exerts inhibitory effects against many human cancer cell lines and provides protection against all stages of carcinogenesis [62]. Research in various cell lines show that vanadium carries out its anticancer effect by inhibiting cellular tyrosine phosphatases and/or activating tyrosine phosphorylases. These effects activate signal transduction pathways culminating either in apoptosis and/or activation of tumor suppressor genes [63].

Vanadium was first found to have antidiabetic properties in 1899 (long before the discovery of insulin in 1921), when orally given sodium vanadate (NaVO3) was found to improve human diabetes mellitus. [64]. Compounds containing vanadium exhibit insulin-like characteristics in vitro and in vivo. At cellular level, vanadium activates several key elements of insulin signal transduction pathway to mediate the metabolic effects of insulin [65].

6. Titanium (Ti): This is another nanoparticle and complex forming anticancer and antidiabetic agent after vanadium.

The first in-depth mechanistic analysis of Ti(IV)- based anticancer drug by genome study of Ti(IV) -Treated cells, showed induction of apoptosis and cell-cycle arrest at the G2/M phase in MCF-7 cells. There was reduced in vitro cytotoxicity and endoplasmic reticulum (ER) stress inhibitor showing the ER as target [66].

Study conducted to investigate the effect of titanium dioxide nanoparticles (TiO2 NPS) on glucose absorption and metabolism in rats for 30 and 90 days showed that oral exposure to TiO2 NPS caused a weak and temporary hypoglycemia in the rats at 30 days post exposure, but recovered at 90 days post exposure [67].

Drug Delivery Systems Overview

These are the methods and technologies that enhance the regulated and targeted delivery of drugs into the body. They find therapeutic uses in oncology and diabetes. This review sets out to identify more specialized applications in diabetic patients having concurrent cancer illness and in cancer patients with glucose intolerance using bifunctional anticancer-antidiabetic vitamins and minerals.

Traditional drug delivery systems include the use of prodrugs, implants and Intrauterine devices, but advances in technology have introduced newer biotechnology-based therapeutics.

They constitute broad classes which include:

1. Vehicles for pharmaceutical delivery
2. Cell and gene therapeutics
3. Pharmaceuticals
4. Biopharmaceuticals
5. vaccines
6. Diagnostics
7. Theranostics

This review will focus only on number 1.

Vehicles for Pharmaceutical Drug Delivery

Drug delivery vehicles are the various methods that medications can be packaged so that they can safely be transported within the body. Examples include micelles, liposomes or nanoparticles. They enhance targeting and give room for packaging hard-to-use drugs [68].

Nanomedicine, nano-delivery and nanotechnology find applications in hemotherapeutics, Diabetology, biological agents, immunotherapeutic etc.

Nanoparticles or nanomaterials which are biodegradable can be proteins, peptides, lipids, metals are materials with sizes ranged between 1 and 100 nm (size similar to that of most biological molecules and structures).

Several anticancer drugs including paclitaxel, doxorubicin, 5-fluorouracil and dexamethasone have been successfully formulated using nanomaterials [69].

Nanoparticles have been researched as vehicles for orally administered insulin formulations. Glucose biosensors equipped with nanoscale materials like Quantum Dots (QDs), Carbon Nanotubes (CNTs), Magnetic Nanoparticles (MNPs) have demonstrated higher sensitivity [70].

Nanoparticles used in drug delivery system and their applications in cancer and diabetes.

1. Polymeric Nanoparticles (PNPs): Polymeric materials used in drug delivery systems. They are made up of non- biodegradable polymers like polyacrylamide, polymethylmethacrylate (PMMA) and polystyrene. Examples of PNPs containing anticancer drugs under development include paclitaxel poliglumex, PEG-camptothecin, HMPA copolymer-platinate, HMPA-copolymer paclitaxel, HMPA copolymer-Doxorubicin.

2. Chitosan: chitosan-based nanomaterials. Application is the release of 5-fluorouracil (5-FU) from hyaluronic acid-coated chitosan nanoparticles into the gut, through oral administration. Insulin proected from enzymatic breakdown using formulations combining chitosan nanoparticles and oleic acid. Glucose sensors (glucose oxidase, boronic acid 4-formylphenylboronic acid etc) have been conjugated with chitosan nanoparticles for glucose-dependent insulin release.

3. Alginate: an anionic mucoadhesive polymer. Insulin- containing alginate nanoparticles with nicotinamide as permeation agent decrease serum glucose and increased serum insulin levels in diabetic rats.

4. Dextran – based nanoparticles: dextran sulfate – chitosan nanoparticles containing insulin reduces blood glucose level.

5. Albumin

6. Xanthan gum: high molecular weight heteropolysaccharide.

7. Monoclonal antibodies nanoparticles

8. Extracellular vesicles

9. Cellulose: cellulose nanocrystals and chitosan used for oral release of repaglinide. Carboxymethylcellulose and alginate used to release 5-FU targeted to the colon.

10. Solid lipid nanoparticles (SLNs): unlike liposomes, SLNs have a micelle-like structure where the drug is entrapped in a non-aqueous core. Examples are mitoxandrone- loaded SLN and doxorubicin and idarubicin SLN incorporation. Various SLN formulations and lecithin as surfactants have been produced for loading insulin.

11. Liposomes: these consist of conventional type liposomes, PEGylated types, ligand – targeted and theranostic types. They can be used with hydrophobic and hydrophilic drugs. Applications are seen with 5-fluoro-deoxyuridine, daunorubicin and doxorubicin. Functionalised liposomes coated with anion polyacrylic acid and cation polyallyl amine hydrochloride created for oral administration of insulin.

12. Nanoemulsions: nanoemulsion consisting of rapamycin, bevacizumab and temozolomide used to treat advanced melanoma.Nanoemulsions contataining α-eleostearic acid orally administered to diabetic rat model with improved antidiabetic properties.
13. Polymeric micelles: made of amphiphilic block copolymers used for paclitaxel, docetaxel.
14. Cyclodextrin nanosponges
15. Carbon nanoparticles
16. Dendrimers: used for targeted drug delivery of doxorubicin and methotrexate.
17. Inorganic nanoparticles: include silver, gold, iron oxide and silica nanoparticles. Iron oxide nanoparticles covered with Violamycine B1 and antracyclinic antibiotics tested against MCF-7 cells for cytotoxicity.
18. Nanocrystals:
19. Metallic nanoparticles: these include gold, silver, iron and copper. Others are Zinc oxide, titanium oxide, platinum, selenium, gadolinium, palladium, cerium dioxide.
20. Magnetic nanoparticles
21. PGLA Based Nanoparticles: for sustained release of insulin.
22. Poly (Lactic Acid) (PLA)-Based nanoparticles: PLA-b-pluronic-b-PLA form vesicle used for oral delivery of insulin.
23. Polyallylamine (PAA) Based nanoparticles: this nanoparticle protected insulin against trypsin and pepsin, showing high encapsulation efficiency.
24. Calcium phosphate nanoparticles
25. Silica nanoparticles
26. Quantum dots: nanometer- scale semiconductors with a broad spectrum of absorption. Quantum dots aptamer- doxorubicin conjugate targets prostate cancer cells.
27. Protein and Polysaccharides nanoparticles [71-73].

Vitamins and Minerals Nano-Based Drug Delivery Systems

Researches in biotechnology deliveries for bifunctional antidiabetic-anticancer vitamins and minerals need to be aggressively pursued, due to the leading roles these agents will definitely play in the future management of both diseases owing to the unique properties of mediating in both diseases signal pathways.

A summary of current advances made in this respect or related fields is given below.

1. Vitamin A: cancer stem cells (CSCs) play key roles in radiotherapy and chemotherapy treatment failures. Retinoic acid enhances differentiation of CSAs. A CSCs-specific targeted, retinoic acid-loaded gold nanostars-dendritic polyglycerol (GNSs-Dpg) nanoplatform has been developed for efficient eradication of CSCs [74]. Sodium alginate possess great drug delivery properties. Retinoic acid (RA) – sodium alginate microspheres (RA-MS) was prepared to slowly release retinoic acid in pharmacotherapy of proliferative vitreoretinopathy. (Lactic acid – glycolic acid copolymer can also serve as carrier for RA) [75].

2. Vitamin C: nano-vitamin combined with paclitaxel inhibited cell over-proliferation. Nano-vitamin C and cisplatin combination used in the management of chemotherapy-associated fatigue. Vitamin C -cisplatin-loaded chitosan nanoparticles enhanced anti-proliferative and anti-angiogenic activity without inhibiting cisplatin anticancer effects [76]. Different nano-vehicles for vit C include nanoliposomes, solid lipid nanoparticles, nanostructured lipid carriers, chitosan nanoparticles, cyclodextrin nanosponges [77].

3. Vitamin D: Both vitamin D and Raloxifene have low bioavailability as a result of reduced solubility. But their bioavailability and pharmacokinetics were increased when both drugs were combined in nanostructure lipid carriers (NLCs) [78]. Calcitriol (promising agent for non-small cell lung cancer) activity is inhibited by 24-hydroxylase. CTA091 is a selective inhibitor of 24-hydroxylase. Calcitriol and CTA091 were loaded in EFFR-targeted liposomes which increased their uptake and inhibition of lung cancer cells [79].

Minerals and Trace Elements Nanocarriers

Many minerals. Trace elements and metals have unique characteristics of been used in complexing with other drugs and as nano-carriers. This unique feature can be explored and exploited in therapeutic management for those which equally have bifunctional anticancer-antidiabetic effect. This will Make these elements play key roles in the management of these diseases.

Several of these metallic nanoparticles have been approved by FDA or EMA for cancer therapy and clinical trials viz: Iron oxide for prostate cancer NCT02033447(Ph 0), Spherical gold nanoparticle for recurrent glioblastoma or gliosarcoma NCT03020017(Ph 0), Hafnium oxide nanoparticle for postoperative pain NCT03692286 (Ph IV), NCT04213716 (PH II) [80].

1. Selenium: selenium nanoparticles (SeNPs) prepared by adding Catatheslasma ventricosum polysaccharides to selenite and ascorbic acid showed higher antidiabetic effects in streptozocin induced diabetic mice than other selenium preparations like SeNPs, selenocysteine, sodium selenite [81].

2. Vanadium: vanadium-based nanomaterials synthesized for cancer treatments include vanadium oxide, 2D vanadium sulfides, carbides and nitides and water insoluble vanadium salts [82].

Bifunctional Vitamins and Mineral Complexes and Combinations in The Management of Daibetes and Cancer.

Aside the use of nano-carriers in the delivery of bifunctional vitamins and minerals, applications can equally be found for therapeutic use of their various combinations.
Complex forming minerals and trace elements like vanadium, titanium, zinc, selenium can be combined with the vitamins to form therapeutic agents. Titanium and vanadium combination complexes have found important therapeutic use in the management of cancer and diabetes, likewise zinc +vanadium, Vitamin A +Vanadium complexes.

Ionophores are also known to increase the intracellular concen-

tration of these agents and increase their bioavailability.

These bifunctional vitamins and minerals can equally be combined with conventional anticancer and antidiabetic agents to enhance their therapeutic efficacy through synergism.

Conclusion

Bifunctional vitamins and minerals with antidiabetic-anticancer effects no doubt have great potentials and roles in the management of cancer and diabetic patients due to their inherent ability to modulate and regulate the signal pathways of both diseases.

These agents on their own and in combination therapies with conventional therapies have markedly increased the therapeutic efficacies of these conventional drugs in the management of both cancer and diabetics.

Drug delivery systems which are technologies for targeted delivery of drugs to the body has a great role to play in enhancing the efficacy and effectiveness of these bifunctional vitamins and minerals by increasing their bioavailability at targeted site.

Other methods of increasing the bioavailability and efficacy of these drugs are by complexing their ions and ionophore aided transport into cells.

Bifunctional anticancer-antidiabetics vitamins and minerals no doubt holds the future in the management of diabetic patients with concurrent cancer illness and cancer patients with glucose intolerance.

References

1. Klaunig, J. E. (2018). Oxidative stress and cancer. Current pharmaceutical design, 24(40), 4771-4778.
2. Zhang, P., Li, T., Wu, X., Nice, E. C., Huang, C., & Zhang, Y. (2020). Oxidative stress and diabetes: antioxidative strategies. Frontiers of medicine, 14, 583-600.
3. Zasowska-Nowak, A., Nowak, P. J., & Ciałkowska-Rysz, A. (2021). High-dose vitamin C in advanced-stage cancer patients. Nutrients, 13(3), 735.
4. Berridge, M. J. (2017). Vitamin D deficiency and diabetes. Biochemical Journal, 474(8), 1321-1332.
5. Schmidt, C. (2014). Low Vitamin D Tied to Aggressive Prostate Cancer. Harvard Health.
6. Paul, M. (2016). Low Vitamin D Predicts Aggressive Prostate Cancer. Northwestern University. ScienceDaily.
7. Cancer Therapy Interactions with Foods and DietarySupplements (PDQ) - Health Professional Version. US National Cancer Institute.
8. Puris L. Vitamins and Cancer Treatment. Cancer Nutrition Consortium.
9. Jain, A., Tiwari, A., Verma, A., & Jain, S. K. (2017). Vitamins for cancer prevention and treatment: an insight. Current molecular medicine, 17(5), 321-340.
10. Jain, K. K. (2020). An overview of drug delivery systems. Drug Delivery Systems, 1-54.
11. Zhao, R., Lu, Z., Yang, J., Zhang, L., Li, Y., & Zhang, X. (2020). Drug delivery system in the treatment of diabetes mellitus. Frontiers in bioengineering and biotechnology, 8, 880.
12. Kim, J., Park, M. K., Li, W. Q., Qureshi, A. A., & Cho, E. (2019). Association of vitamin A intake with cutaneous squamous cell carcinoma risk in the United States. JAMA dermatology, 155(11), 1260-1268.
13. Vitamin, A. (2015). Cancer Treatment and Prevention: The New Role of Cellular Retinol Binding Proteins/E. Doldo et al. Biomed Res Int.
14. Zhang, Y., Wang, T., Hu, X., & Chen, G. (2021). Vitamin A and diabetes. Journal of Medicinal Food, 24(8), 775-785.
15. Iqbal, S., & Naseem, I. (2015). Role of vitamin A in type 2 diabetes mellitus biology: effects of intervention therapy in a deficient state. Nutrition, 31(7-8), 901-907.
16. Chen, G. (2021). The interactions of insulin and Vitamin A signaling systems for the regulation of hepatic glucose and lipid metabolism. Cells, 10(8), 2160.
17. Chen, A. C., Martin, A. J., Choy, B., Fernández-Peñas, P., Dalziell, R. A., McKenzie, C. A., ... & Damian, D. L. (2015). A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. New England journal of medicine, 373(17), 1618-1626.
18. Park, S. M., Li, T., Wu, S., Li, W. Q., Weinstock, M., Qureshi, A. A., & Cho, E. (2017). Niacin intake and risk of skin cancer in US women and men. International journal of cancer, 140(9), 2023-2031.
19. Goun, E. et al. (2022). New Imaging Technique in Animal Study Gives Insight into Popular Supplement's Potential Role in Cancer Progression. University of Missouri-Columbia.
20. Abdullah, K. M., Alam, M. M., Iqbal, Z., & Naseem, I. (2018). Therapeutic effect of vitamin B3 on hyperglycemia, oxidative stress and DNA damage in alloxan induced diabetic rat model. Biomedicine & Pharmacotherapy, 105, 1223-1231.
21. Brenner, C. et al. (2016). Vitamin Nicotinamide Riboside Protects Mice from Diabetes Complications. University of Iowa Health Care.
22. Van Der Reest, J., & Gottlieb, E. (2016). Anti-cancer effects of vitamin C revisited. Cell research, 26(3), 269-270.
23. Butt, G., Farooqi, A. A., Adylova, A., Attar, R., Yilmaz, S., Konysbayevna, K. K., ... & Xu, B. (2020). Vitamin C as an anticancer agent: regulation of signaling pathways. Current topics in medicinal chemistry, 20(21), 1868-1875.
24. Afkhami-Ardekani, M., & Shojaoddiny-Ardekani, A. (2007). Effect of vitamin C on blood glucose, serum lipids & serum insulin in type 2 diabetes patients. Indian Journal of medical research, 126(5), 471-474.
25. Mason, S. A., Keske, M. A., & Wadley, G. D. (2021). Effects of vitamin C supplementation on glycemic control and cardiovascular risk factors in people with type 2 diabetes: a GRADE-assessed systematic review and meta-analysis of randomized controlled trials. Diabetes Care, 44(2), 618-630.
26. Muñoz, A., & Grant, W. B. (2022). Vitamin D and cancer: an historical overview of the epidemiology and mechanisms. Nutrients, 14(7), 1448.
27. Chen, J., Tang, Z., Slominski, A. T., Li, W., Żmijewski, M.

A., Liu, Y., & Chen, J. (2020). Vitamin D and its analogs as anticancer and anti-inflammatory agents. European journal of medicinal chemistry, 207, 112738.
28. Alvarez, J. A., & Ashraf, A. (2010). Role of vitamin D in insulin secretion and insulin sensitivity for glucose homeostasis. International journal of endocrinology, 2010.
29. Esteghamati, A., Aryan, Z., Esteghamati, A. R., & Nakhjavani, M. (2015). Vitamin D deficiency is associated with insulin resistance in nondiabetics and reduced insulin production in type 2 diabetics. Hormone and Metabolic Research, 47(04), 273-279.
30. Abraham, A., Kattoor, A. J., Saldeen, T., & Mehta, J. L. (2019). Vitamin E and its anticancer effects. Critical reviews in food science and nutrition, 59(17), 2831-2838.
31. Kline, K., Lawson, K. A., Yu, W., & Sanders, B. G. (2007). Vitamin E and cancer. Vitamins & Hormones, 76, 435-461.
32. BABURAO JAIN, A. N. A. N. D., & ANAND JAIN, V. A. I. S. H. A. L. I. (2012). Vitamin E, Its Beneficial Role in Diabetes Mellitus (DM) and Its Complications. Journal of Clinical & Diagnostic Research, 6(10).
33. Goldenstein, H., Levy, N. S., Lipener, Y. T., & Levy, A. P. (2013). Patient selection and vitamin E treatment in diabetes mellitus. Expert review of cardiovascular therapy, 11(3), 319-326.
34. Suksomboon, N., Poolsup, N., & Sinprasert, S. (2011). Effects of vitamin E supplementation on glycaemic control in type 2 diabetes: systematic review of randomized controlled trials. Journal of clinical pharmacy and therapeutics, 36(1), 53-63.
35. Gul, S., Maqbool, M. F., Maryam, A., Khan, M., Shakir, H. A., Irfan, M., ... & Ma, T. (2022). Vitamin K: A novel cancer chemosensitizer. Biotechnology and Applied Biochemistry, 69(6), 2641-2657.
36. Shibayama-Imazu, T., Aiuchi, T., & Nakaya, K. (2008). Vitamin K2-mediated apoptosis in cancer cells: Role of mitochondrial transmembrane potential. Vitamins & Hormones, 78, 211-226.
37. Wellington, K. W., Hlatshwayo, V., Kolesnikova, N. I., Saha, S. T., Kaur, M., & Motadi, L. R. (2020). Anticancer activities of vitamin K3 analogues. Investigational New Drugs, 38, 378-391.
38. Li, Y., peng Chen, J., Duan, L., & Li, S. (2018). Effect of vitamin K2 on type 2 diabetes mellitus: A review. Diabetes research and clinical practice, 136, 39-51.
39. Karamzad, N., Maleki, V., Carson-Chahhoud, K., Azizi, S., Sahebkar, A., & Gargari, B. P. (2020). A systematic review on the mechanisms of vitamin K effects on the complications of diabetes and pre-diabetes. Biofactors, 46(1), 21-37.
40. Skrajnowska, D., & Bobrowska-Korczak, B. (2019). Role of zinc in immune system and anti-cancer defense mechanisms. Nutrients, 11(10), 2273.
41. Ananda, S. P., Frances, W. J., Diane, C. S., & Omer, K. (2009). Zinc in cancer prevention. Nutrition and Cancer, 61(6), 879-887.
42. Prasad, A. S., Beck, F. W., Grabowski, S. M., Kaplan, J., & Mathog, R. H. (1997). Zinc deficiency: changes in cytokine production and T-cell subpopulations in patients with head and neck cancer and in noncancer subjects. Proceedings of the Association of American Physicians, 109(1), 68-77.
43. Vardatsikos, G., Pandey, N. R., & Srivastava, A. K. (2013). Insulino-mimetic and anti-diabetic effects of zinc. Journal of inorganic biochemistry, 120, 8-17.
44. Jayawardena, R., Ranasinghe, P., Galappatthy, P., Malkanthi, R. L. D. K., Constantine, G. R., & Katulanda, P. (2012). Effects of zinc supplementation on diabetes mellitus: a systematic review and meta-analysis. Diabetology & metabolic syndrome, 4(1), 1-12.
45. Kuršvietienė, L., Mongirdienė, A., Bernatonienė, J., Šulinskienė, J., & Stanevičienė, I. (2020). Selenium anticancer properties and impact on cellular redox status. Antioxidants, 9(1), 80.
46. Zeng, H., & Combs Jr, G. F. (2008). Selenium as an anticancer nutrient: roles in cell proliferation and tumor cell invasion. The Journal of nutritional biochemistry, 19(1), 1-7.
47. Radomska, D., Czarnomysy, R., Radomski, D., & Bielawski, K. (2021). Selenium compounds as novel potential anticancer agents. International Journal of Molecular Sciences, 22(3), 1009.
48. Bleys, J., Navas-Acien, A., & Guallar, E. (2007). Serum selenium and diabetes in US adults. Diabetes care, 30(4), 829-834.
49. Kohler, L. N., Foote, J., Kelley, C. P., Florea, A., Shelly, C., Chow, H. S., ... & Jacobs, E. T. (2018). Selenium and type 2 diabetes: systematic review. Nutrients, 10(12), 1924.
50. Lv, M., Chen, M., Zhang, R., Zhang, W., Wang, C., Zhang, Y., ... & Jiang, Z. (2020). Manganese is critical for antitumor immune responses via cGAS-STING and improves the efficacy of clinical immunotherapy. Cell Research, 30(11), 966-979.
51. Hernroth, B., Holm, I., Gondikas, A., & Tassidis, H. (2018). Manganese inhibits viability of prostate cancer cells. Anticancer Research, 38(1), 137-145.
52. Chen, X. B., Wei, Y. H., Chen, X. K., Zhong, J., Zou, Y. B., & Nie, J. Y. (2019). Manganese levels and hepatocellular carcinoma: A systematic review and meta-analysis based on Asian cohort. Medicine, 98(32).
53. Manganese for Type 2 Diabetes. Biomify Microbiome Health, 2018.
54. Lee, S. H., Jouihan, H. A., Cooksey, R. C., Jones, D., Kim, H. J., Winge, D. R., & McClain, D. A. (2013). Manganese supplementation protects against diet-induced diabetes in wild type mice by enhancing insulin secretion. Endocrinology, 154(3), 1029-1038.
55. Baly, D. L., Curry, D. L., Keen, C. L., & Hurley, L. S. (1984). Effect of manganese deficiency on insulin secretion and carbohydrate homeostasis in rats. The Journal of nutrition, 114(8), 1438-1446.
56. Hurley, L. S., Keen, C. L., Baly, D.L. (1984). Manganese Deficiecy and Toxicity: Effect on Carbohydrate Metabolism in the Rat. Neurotoxicology Spring, 5(1), 97-104.
57. Du, S., Wu, X., Han, T., Duan, W., Liu, L., Qi, J., ... & Sun, C. (2018). Dietary manganese and type 2 diabetes mellitus: two prospective cohort studies in China. Diabetologia, 61, 1985-1995.
58. Yoshiji, H., Kuriyama, S., Yoshii, J., Ikenaka, Y., Noguchi, R., Yanase, K., ... & Fukui, H. (2003). The copper-chelating

agent, trientine, attenuates liver enzyme-altered preneoplastic lesions in rats by angiogenesis suppression. Oncology reports, 10(5), 1369-1373.
59. Yoshii, J., Yoshiji, H., Kuriyama, S., Ikenaka, Y., Noguchi, R., Okuda, H., ... & Fukui, H. (2001). The copper-chelating agent, trientine, suppresses tumor development and angiogenesis in the murine hepatocellular carcinoma cells. International journal of cancer, 94(6), 768-773.
60. Tanaka, A., Kaneto, H., Miyatsuka, T., Yamamoto, K., Yoshiuchi, K., Yamasaki, Y., ... & Matsuhisa, M. (2009). Role of copper ion in the pathogenesis of type 2 diabetes. Endocrine journal, 56(5), 699-706.
61. Qiu, Q., Zhang, F., Zhu, W., Wu, J., & Liang, M. (2017). Copper in diabetes mellitus: a meta-analysis and systematic review of plasma and serum studies. Biological trace element research, 177, 53-63.
62. Bishayee, A., Waghray, A., Patel, M. A., & Chatterjee, M. (2010). Vanadium in the detection, prevention and treatment of cancer: the in vivo evidence. Cancer Letters, 294(1), 1-12.
63. Evangelou, A. M. (2002). Vanadium in cancer treatment. Critical reviews in oncology/hematology, 42(3), 249-265.
64. Sakurai, H. (2002). A new concept: the use of vanadium complexes in the treatment of diabetes mellitus. The Chemical Record, 2(4), 237-248.
65. Srivastava, A. K., & Mehdi, M. Z. (2005). Insulino-mimetic and anti-diabetic effects of vanadium compounds. Diabetic medicine, 22(1), 2-13.
66. Miller, M., Mellul, A., Braun, M., Sherill-Rofe, D., Cohen, E., Shpilt, Z., ... & Tabach, Y. (2020). Titanium tackles the endoplasmic reticulum: a first genomic study on a titanium anticancer metallodrug. Iscience, 23(7), 101262.
67. Chen, Z., Wang, Y., Wang, X., Zhuo, L., Chen, S., Tang, S., ... & Jia, G. (2018). Effect of titanium dioxide nanoparticles on glucose homeostasis after oral administration. Journal of Applied Toxicology, 38(6), 810-823.
68. National Instuitute of Biomedical Imaging and Bioengineering. Drug Delivery Sytems, 2022.
69. Suri, S. S., Fenniri, H., & Singh, B. (2007). Nanotechnology-based drug delivery systems. Journal of occupational medicine and toxicology, 2, 1-6.
70. Siwach, R., Pandey, P., Chawla, V., & Dureja, H. (2019). Role of nanotechnology in diabetic management. Recent patents on nanotechnology, 13(1), 28-37.
71. Patra, J. K., Das, G., Fraceto, L. F., Campos, E. V. R., Rodriguez-Torres, M. D. P., Acosta-Torres, L. S., ... & Shin, H. S. (2018). Nano based drug delivery systems: recent developments and future prospects. Journal of nanobiotechnology, 16(1), 1-33.
72. Gavas, S., Quazi, S., & Karpiński, T. M. (2021). Nanoparticles for cancer therapy: current progress and challenges. Nanoscale research letters, 16(1), 173.
73. Souto, E. B., Souto, S. B., Campos, J. R., Severino, P., Pashirova, T. N., Zakharova, L. Y., ... & Santini, A. (2019). Nanoparticle delivery systems in the treatment of diabetes complications. Molecules, 24(23), 4209.
74. Pan, Y., Ma, X., Liu, C., Xing, J., Zhou, S., Parshad, B., ... & Haag, R. (2021). Retinoic acid-loaded dendritic polyglycerol-conjugated gold nanostars for targeted photothermal therapy in breast cancer stem cells. ACS nano, 15(9), 15069-15084.
75. Wang, F., He, S., & Chen, B. (2018). Retinoic acid-loaded alginate microspheres as a slow release drug delivery carrier for intravitreal treatment. Biomedicine & Pharmacotherapy, 97, 722-728.
76. Bedhiafi, T., Idoudi, S., Fernandes, Q., Al-Zaidan, L., Uddin, S., Dermime, S., ... & Merhi, M. (2023). Nano-vitamin C: A promising candidate for therapeutic applications. Biomedicine & Pharmacotherapy, 158, 114093.
77. Comunian, T., Babazadeh, A., Rehman, A., Shaddel, R., Akbari-Alavijeh, S., Boostani, S., & Jafari, S. M. (2022). Protection and controlled release of vitamin C by different micro/nanocarriers. Critical Reviews in Food Science and Nutrition, 62(12), 3301-3322.
78. Hosny, K. M., Bahmdan, R. H., Alhakamy, N. A., Alfaleh, M. A., Ahmed, O. A., & Elkomy, M. H. (2020). Physically optimized nano-lipid carriers augment raloxifene and vitamin d oral bioavailability in healthy humans for management of osteoporosis. Journal of Pharmaceutical Sciences, 109(7), 2145-2155.
79. Glowka, E., Stasiak, J., & Lulek, J. (2019). Drug delivery systems for vitamin D supplementation and therapy. Pharmaceutics, 11(7), 347.
80. Chandrakala, V., Aruna, V., & Angajala, G. (2022). Review on metal nanoparticles as nanocarriers: Current challenges and perspectives in drug delivery systems. Emergent Materials, 1-23.
81. Liu, Y., Zeng, S., Liu, Y., Wu, W., Shen, Y., Zhang, L., ... & Wang, C. (2018). Synthesis and antidiabetic activity of selenium nanoparticles in the presence of polysaccharides from Catathelasma ventricosum. International journal of biological macromolecules, 114, 632-639.
82. Hu, D., Li, D., Liu, X., Zhou, Z., Tang, J., & Shen, Y. (2020). Vanadium-based nanomaterials for cancer diagnosis and treatment. Biomedical Materials, 16(1), 014101.