1st International Congress on Cancer Prevention
ICCP 2024
Zanjan, Iran
18-19 September 2024
University of Zanjan

Effectiveness of using nutrient nanoparticles in cancer prevention

Maryam Heydari , Sajedeh Eghbali , Zahra Rezvani *

department of cell and molecular biology, faculty of chemistry, University of Kashan, Kashan, Iran

* Corresponding Author: Rezvani@kashanu.ac.ir

Abstract

Preventing cancer means suppressing, reversing and preventing cancer cells from becoming aggressive. the use of nutrients that have medicinal benefits and help reduce signal transduction pathways that are necessary for cancer development; But their poor solubility in water, which leads to their poor oral bioavailability, limits their clinical effectiveness. The emergence of nanotechnology has provided an opportunity that can be effective in the diagnosis, prevention and treatment of cancer. The use of nutrients in nano sizes helps to greatly reduce the limitations (stability, solubility, toxicity) of using nutrients in conventional ways. During the past several decades, compounds such as flavonoid, curcumin, taxol, etc. have been preventive factors in cancer; For the reasons mentioned, their use is limited. By overcoming these limitations (encapsulation and other nanotechnology methods), these materials can be used in the best possible way. The resulting research shows the production of various nutrients such as curcumin, taxol, etc. in the form of nanoparticles. It is expected that with the efforts of researchers in the nano field and progress in nanotechnology, she will achieve a variety of standard drugs in the treatment and prevention of cancer.

Keywords: Taxol, cancer, encapsulation, curcumin, nanotechnology

1- Introduction

According to estimates by the American Cancer Society, cancer is the second leading cause of death in the United States, and about one-third of cancers are attributable to preventable lifestyle factors such as poor diet, excessive alcohol consumption, inactivity, and being overweight.[1] In addition to the fact that you can prevent cancer by modifying your lifestyle; Another approach makes this possible through the administration of nutrients. Nutraceutical is a term of nutrition and pharmaceuticals coined by Stephen L. Defelice, president of the Foundation (FIM) in 1989. He as a definition; Nutrients are defined as any substance that is a food or a part of food. Recently, these substances have received attention in the field of cancer research due to their pleiotropic and non-toxic effects. [1] .[2] Many natural products have been studied for their effectiveness on molecular pathways for cancer prevention and treatment. Curcumins, resveratrols, gallates, taxols, etc. are among these products that are used in the treatment and prevention of cancer.[3] Some properties of these materials such as solubility, stability and poor bioavailability limit the use of these products.[3] Natural products are valuable bioactive sources used in modern medicine due to their potential ability to suppress cancer.[4] Nutrients, by affecting the signaling pathways, prevent the proliferation of cancer cells and induce apoptosis and stop the cell cycle; It suppresses invasion, metastasis and angiogenesis.[1] To overcome these limitations, researchers reduce these limitations with the help of nano technology and nano-based encapsulation and increase the bioavailability of these products.[5] With the emergence of nanotechnology and different encapsulation methods, it is expected that achievements will be made in the production of standard drugs for the treatment of various cancers.[5]

2- Methodology

Nutrients and cancer prevention

A number of nutrients are used to prevent cancer. But due to their poor solubility in water, poor permeability, which leads to poor bioavailability in humans; Their use has limitations. Also, processes such as 1. limited release from the food matrix, 2. formation of insoluble complexes with other components in the digestive system (GTI) and 3. biological transformation in GTI can affect the poor bioavailability of these substances. There are some reasons that cause the failure of chemotherapy using natural products in clinical trials: 1. The diverse genetic background of the patients, 2. The diverse dietary habits of the patients and 3. Inefficient systemic delivery and poor bioavailability.[1, 3] To solve this problem, researchers have introduced pharmaceutical platforms based on nanocarriers, which can overcome these challenges due to their high surface-to-volume ratio, nanoparticle size, and appropriate physicochemical properties. There are different types of nanocarriers, which include polymeric nanoparticles, micelles, liposomes, etc.[1] The mechanisms through which nutrients can prevent cancer include inhibition of cell proliferation and differentiation, inhibition of outgoing transporters such as breast cancer resistance protein (BCRP), glycoproteins, multidrug resistance proteins (MRP), etc.[1]Nutrients enable cancer prevention through miRNA modulation, cell signaling and epigenome. These substances are pleiotropic and reduce various signaling pathways, which makes them effective agents for inhibiting carcinogenesis and effective cancer treatment.[1] Curcumins and resveratrols are used as two polyphenols in the diet due to their antioxidant properties. In addition to in vitro and in vivo research, these two substances have also entered clinical research. It has been shown that these two natural compounds, in addition to being used in chemotherapy, in combination with a series of chemotherapy agents such as docetaxel, doxorubicin, etc., have a good potential to be used as anti-cancer drugs without causing side effects. Also, the research shows the protective effect of these two compounds and the reduction of drug resistance by it.[2] Curcumin inhibits cell proliferation by inducing cell cycle arrest in the G2/M phase of U373MG and U87MG malignant glioma cells. It also regulates p70SK/mTOR/AKT pathways to induce autophagic cell death. Curcumin induces caspase-3-dependent apoptosis in MG-63 cells. Also, curcumin-dependent treatment causes the expression of JNK and Bcl2 in MG-63 cells, which induces the initiation of apoptosis.[2] Initiation of apoptosis and autophagy has been observed in MCF7 breast cancer and PC3 and DU145 prostate cancer cells during curcumin treatment. It has also been found that curcumin treatment causes positive activation of Bax, reduction of Bcl2 and activation of caspase 9. Treatment of A549 human lung adenocarcinoma cells with curcumin regulates autophagy by affecting AMPK, MAPK and ERK1/2 signaling pathways related to cell survival and cell death.[2] The emergence of nanotechnology in the 21st century created an opportunity to provide new ways to diagnose, prevent and treat various diseases, especially cancer. Compounds in nano sizes are suitable platforms for delivering drugs and various substances to the desired location without harming the activity of the desired drug. The use of natural substances at the nanoscale allows us to improve many of the limitations mentioned (solubility, stability, toxicity, poor bioavailability).[3]

1. **Types of nano formulations**:

To choose a suitable formulation, the solubility of the drug to be loaded should be considered. Two suitable carriers for this work are liposomes (to carry water-soluble drugs) and micelles (to carry water-insoluble drugs).[5] Liposomes are artificial phospholipid vesicles with a size usually less than 1000 nm, which are loaded with various water-soluble drugs. Among their biological properties, we can mention their biocompatibility and non-toxicity. Drugs loaded in liposomes are immune to external factors.[5] The use of curcumins, resveratrols, EGCG, etc., due to their hydrophobicity and low solubility in water, causes bioavailability and weak absorption, and these limitations bring problems. Therefore, micelles, including polymer micelles, are one of the suitable options for transporting drugs. Micelles are particles with a size of 5-100 nm.

Micelles can increase the solubility and improve the bioavailability of poorly soluble drugs. Due to their small size, they show spontaneous permeability into body compartments with leaky vessels.[5] One of the important challenges in cancer treatment is the lack of targeted delivery of drugs to cancer tissue. Nanomedicines are a new and targeted tool to improve the process of cancer treatment.[6] Nanoparticles can contribute to this by increasing stability, increasing half-life in blood circulation, and increasing deposition inside the tumor. In addition, nanoparticles are used as carriers for imaging probes (probes are placed inside nanoparticles) and the desired data on non-target accumulation sites in healthy tissue and drug side effects are investigated. There is a wide range of nanoparticles that are effective in the development of cancer drugs, among which synthetic lipids, synthetic polymers, etc. can be mentioned.[6].

1. Materials and compounds with nano formulation:

1.1. Curcumin and resveratrol as synergistic agents in cancer chemotherapy:

During the studies, it was found that the administration of curcumin along with several chemotherapy agents was effective in increasing the anti-cancer activity. Curcumin in combination with cisplatin inhibited the phosphorylation of ERK signaling pathway and its antitumor activity increased. Curcumin combined with doxorubicin showed chemotherapy sensitivity by arresting the cell cycle and inducing apoptotic cell death, and it was found that curcumin induced the intracellular accumulation of doxorubicin through the reduction of P-glycoprotein, which increases anticancer activity.[2] It was found that resveratrol as a natural compound increases the antitumor effects of chemotherapy drugs in vitro and in vivo. The potent antitumor effects of the combination of resveratrol and rapamycin were well demonstrated in various cancer cell lines and in vivo tumor models. Rapamycin and resveratrol increased antitumor efficacy by inducing autophagy by reducing AKT phosphorylation in breast cancer cell lines.[2]

1.2. Curcumin:

One of the products that has been studied in the nano field is curcumins. The main curcuminoid of Indian turmeric grows in Southeast Asia. As a compound, curcumins are mainly derived from turmeric and have been used as a convenient medicine for centuries. Its biological activities such as antioxidant, apoptotic and anti-inflammatory effects make curcumin suitable for cancer treatment. Research has shown that curcumin is effective in treating cancers such as multiple myeloma, pancreas, myelodysplastic syndromes, colon and psoriasis. [3, 5, 7] Despite the effectiveness of this compound, rapid degradation and poor bioavailability in biological systems are among the challenges facing the use of this compound at the clinical level.[5] In a study by Bisht et al. Cross-linked and random copolymers of N-isopropylacrylamide (NIPAAM) with N-vinyl-2-pyrrolidine nanoparticles and polyethylene glycol monoacrylate (PEG A) were effectively combined with curcumin and nanoparticles with a size of about 50 nm were obtained.[8] The data showed the effectiveness of nanoformulated curcumin compared to free curcumin in dealing with pancreatic cancer cell lines. It was also observed that nano-encapsulated curcumin, like free curcumin, can induce cell apoptosis and decrease the stable level of several pro-inflammatory cytokines IL6, IL8 and TNFα.[3] During recent years and more studies by researchers, they have been able to achieve better results. Recent studies on curcumin in various cancers such as stomach, cervix, Hcc, etc., have determined that curcumin consumption can cause DNA damage, stop the cell cycle in the G2/M phase in HeLa cells. Also, curcumin in liver cancer can prevent the proliferation of different cell lines and induce HepG2 cell apoptosis by increasing ROS and regulating the TGFβ1/smad3 signaling pathway.[7] Despite its poor bioavailability, curcumin was used in the first phase clinical trials for colorectal, breast, pancreatic cancer, etc. In studies, the safety and non-toxicity of absorbing high doses of curcumin (8 grams per day) was proven. As an experiment, it was shown that the combination of gemistabine with curcumin (2000 mg) per day is a more effective treatment compared to the use of gemistabine alone.[2] In the second phase of other clinical trials (NCT00094445), it was observed that taking curcumin in the form of oral tablets daily for up to 8 weeks in patients with adenocarcinoma or advanced pancreatic cancer increased patient survival. Also, a significant increase in IL6, IL8, IL10 and a decrease in pSTAT3, NFκβ and Cox2 were observed.[2]

1.3. Resveratrol:

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is introduced as a polyphenol that has natural antioxidant properties and is found in various plants such as grapes, peanuts and berries. This natural composition is used by some plants during the attacks of foreign phytogens such as fungi and bacteria to fight and repair. [3, 7] Recent studies show that resveratrol is effective in preventing the development of cancers such as breast, colorectal, pancreatic, prostate and liver cancer. For example, in breast cancer, resveratrol prevents the proliferation of cells by regulating the STAT3 signaling cascade with antioxidant and anti-inflammatory effects.[7] Resveratrol has a molecular weight of 25.228 g/mol and a melting point of 254 degrees Celsius. Despite the chemical properties that this substance introduces as a cancer preventive agent, due to its low bioavailability and chemical instability, it creates various pharmacokinetic challenges. Contrary to the absorption of 75% of this compound after oral intake by the intestinal epithelium and through passive diffusion, it has been shown that this natural compound is metabolized in the intestine and liver and metabolites trans-resveratrol-3-O-glucuronide and trans-resveratrol- 3-sulfate is converted.[6] For the first time, nanoformulation of resveratrol with chitosan was done, this study by Yao et al. Was obtained. They prepared resveratrol chitosan nanoparticles with free surface amine groups to attach ligands that actively target specific tissues and organs. [3, 9] Solid lipid nanoparticles (SLN) were used as resveratrol carrier in another study. The effects of empty SLN (RSV-free) or loaded with resveratrol (SLN RSV) on the growth, morphology, metabolic activity and genetic material of keratinocytes were compared with soluble resveratrol. The results show more effect of SLN RSV than soluble RSV. The delivery of RSV by SLN contributes to the effectiveness of this natural compound in reducing cell proliferation and has a good effect in preventing skin cancer.[5] Resveratrol induces apoptosis of malignant liver tissue by activating caspase 3, upregulating Bax/Bcl2 ratio and increasing P53 expression. It was also found in studies that the combination of curcumin or resveratrol with cisplatin is effective in the treatment of various cancers and reduces the chemical resistance and side effects of cisplatin.[7] In the first phase of prostate cancer treatment with resveratrol, it was observed that treatment with resveratrol (4 grams per day) moderated the PSA level. After treatment with resveratrol, the doubling time of PSA is probably increased by 3.5 months. In a clinical trial in phase I (NCT002556334) resveratrol consumption for 2 weeks and in the amount of 80-120 grams per day in patients with colon cancer, colon tumor growth was reduced in patients through regulating the Wnt signaling pathway.[2] During research, it has been observed that treatment of human colon cancer cells COLO201 and HT-29 with resveratrol induces apoptosis through excessive accumulation of ROS. It also enables the initiation of apoptosis by activating caspases 3 and 8. Resveratrol induces autophagic cell death in five apoptosis resistant ovarian cancer cell lines by regulating PIK3, AKT/mTOR signaling pathway. It has been observed that the modulation of the extrinsic apoptotic death receptor fas and its ligand fasL causes the initiation of apoptotic cell death in leukemia cells treated with resveratrol. Intrinsic apoptotic was also suggested with upregulation of Bax and reduction of bcl2 in cells treated with resveratrol. In a study conducted on chronic myeloid leukemia cells, resveratrol regulates the JNK/AMPK/mTOR signaling pathway.[2]

1.4. Taxol:

Taxol was recognized as a natural compound and as one of the 3 important anticancer drugs in the 1990s. Taxol's action is primarily to induce microtubule spindle dynamics and to control cell proliferation and DNA repair. Unlike other anti-mitotic drugs, taxols, by acting on tubulin, block or inhibit mitosis instead of tumor cells and have no effect on the division of tumor cells, and as a result, this substance has fewer side effects. Experiments show that Taxol can remain in the tumor for 20 hours and inhibit tumor growth by affecting the proliferation of tumor cells.[10] This substance is mainly used in the treatment of ovarian and breast cancers and has effects on lung, colorectal, melanoma, head and neck and lymphoma. Also, by effecting the mitotic arrest, Taxol induces cell apoptosis, activates macrophages, and regulates the function of the immune system. [10]The use of this natural compound has limitations despite its clinical success. Taxol is insoluble in water, and to solve this problem, they use ethanol and Cremophor EL, which has certain side effects.[3] To overcome the solubility challenge, Onyukse and his group created the first nano formulation by using spatially stabilized phospholipid micelles (SSMs) consisting of ethylene glycol 2000, distearoyl phosphatidyl ethanolamine (PEG (2000) (DSPE)) as New lipid-based conjugated carriers for water-insoluble drugs. They compared spatially stabilized composite micelles (SSMM) consisting of (PEG (2000) (DSPE)) plus egg phosphatidylcholine with SSM (delivery system to improve water-insoluble solubility) as a model. The results of this study show that SSMM has more dissolution potential than SSM and has not lost its advantages.[11]

4- Conclusions

Nanotechnology is considered as a suitable option for cancer prevention. Researchers have been able to solve the challenges related to the use of natural compounds (solubility, stability, dehydration and poor bioavailability) with nano technology and the creation of nanoscale compounds. So far, researchers have been able to nanoformulate natural compounds such as resveratrol, curcumin, etc. with different methods and enable their use without existing challenges and limitations. Nanocapsulated curcumins prevent and treat various cancers, including pancreatic cancer, colon cancer, myelodysplastic syndromes, etc., by affecting apoptosis and reducing the level of pro-inflammatory cytokines. Growth and proliferation of cancer cells. Resveratrol acts as a strong antioxidant and is an anti-cancer agent in stomach, lung, skin, and breast cancers. It has been observed that the loading of this material with nanocarriers such as SLNs has an effect on the growth, morphology and metabolism of cancer cell lines. In the case of taxols, this natural compound is effective against leukemia, solid breast tumors, lung, brain cancers, etc., and this substance is considered one of the first chemotherapy drugs approved by the FDA. In general, the studies conducted in this field show the high potential of nanotechnology and nanoformulation as carriers to provide nutrients. Of course, in order to realize this, more clinical trials and research are needed.

References

1. Arora, D. and S. Jaglan, *Nanocarriers based delivery of nutraceuticals for cancer prevention and treatment: A review of recent research developments.* Trends in Food Science & Technology, 2016. **54**: p. 114-126.

2. Patra, S., et al. *Chemotherapeutic efficacy of curcumin and resveratrol against cancer: Chemoprevention, chemoprotection, drug synergism and clinical pharmacokinetics*. in *Seminars in cancer biology*. 2021. Elsevier.
3. Bharali, D.J., et al., *Nanoparticle delivery of natural products in the prevention and treatment of cancers: current status and future prospects.* Cancers, 2011. **3**(4): p. 4024-4045.
4. Nair, H.B., et al., *Delivery of antiinflammatory nutraceuticals by nanoparticles for the prevention and treatment of cancer.* Biochemical pharmacology, 2010. **80**(12): p. 1833-1843.
5. Muqbil, I., et al., *Progress in nanotechnology based approaches to enhance the potential of chemopreventive agents.* Cancers, 2011. **3**(1): p. 428-445.
6. Annaji, M., et al., *Resveratrol-loaded nanomedicines for cancer applications.* Cancer reports, 2021. **4**(3): p. e1353.
7. Zheng, Y., et al., *Curcumin-and resveratrol-co-loaded nanoparticles in synergistic treatment of hepatocellular carcinoma.* Journal of Nanobiotechnology, 2022. **20**(1): p. 339.
8. Bisht, S., et al., *Polymeric nanoparticle-encapsulated curcumin (" nanocurcumin"): a novel strategy for human cancer therapy.* Journal of nanobiotechnology, 2007. **5**: p. 1-18.
9. Yao, Q., et al., *Study on the preparation of resveratrol chitosan nanoparticles with free amino groups on the surface.* Zhongguo Zhong Yao Za Zhi= Zhongguo Zhongyao Zazhi= China Journal of Chinese Materia Medica, 2006. **31**(3): p. 205-208.
10. Yan-Hua, Y., M. Jia-Wang, and T. Xiao-Li, *Research progress on the source, production, and anti-cancer mechanisms of paclitaxel.* Chinese Journal of Natural Medicines, 2020. **18**(12): p. 890-897.
11. Krishnadas, A., I. Rubinstein, and H. Önyüksel, *Sterically stabilized phospholipid mixed micelles: in vitro evaluation as a novel carrier for water-insoluble drugs.* Pharmaceutical research, 2003. **20**: p. 297-302.