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The Role of Natural Dietary Products in Nanomedicine

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Abstract

It has long been established that a diet rich in fresh fruits, vegetables, seeds, grains and legumes and antioxidants, and other beneficial compounds may help prevent various human diseases. However, diet is not a cure for treatment of severe diseases, but it may help prevent some ailments, and it can help the body overcome the effects of conventional treatments. Natural compounds not only serve as a drug or template for drugs but also, in many instances, had been a source of discovery of novel biology that provided better understanding of target and pathway involved in the disease processes. In addition, drugs derived from natural compounds work better for patients than do drugs manufactured synthetically. Approximately, 40% of drugs in the pipeline and 70% of synthetic therapeutic molecules are plagued with poor solubility, oral bioavailability, and delivery. Drugs with poor solubility encounter limited transport during oral administration because of low concentration gradient between the gut and the blood vessels. To increase body fluid saturation solubility of poorly soluble drug, new delivery methods need to be developed using natural dietary plant metabolites.

Keywords: plant metabolite, human ailments, disease therapy, nanomedicine

1. Introduction

1.1. Natural dietary products

Natural product therapeutic compound is a substance or compound produced by living organisms which has pharmacological or biological activity and with potential to be developed into

new pharmaceuticals. Natural products may be extracted from plant tissues, marine organisms or microorganism fermentation broths by various mechanical methods [1, 2].

The earliest records of natural products and oldest medical text come from ancient Mesopotamia corresponding to modern-day Iraq (2600 BC), which is written on hundreds of clay tablets in cuneiform. The tablets describe approximately 1000 plants and plant-derived substances, such as the oils of *Cedrus* species (cedar), resin of *Commiphora myrrha* (myrrh), and juice of the poppy seed *Papaver somniferum* with therapeutic potential [3]. The Chinese were the first to use medicinal plants from which over 11,000 herbal remedies were developed and used for thousands of years. In India, natural products are generally accepted as the main disease treatment method, as such almost 70% modern medicines in India are derived from natural products [2].

According to the recent WHO studies, over 30% of plant species of the world have been used for medicinal purposes. Among the estimated 250,000–500,000 higher plant species on earth, more than 80,000 species are purported to possess medicinal properties. However, only a small percentage of these plants has been investigated phytochemically [2]. Some natural compounds are already known to be useful drugs and these include alkaloids, morphine, and quinine, while others such as cocaine have been the basis for synthetic drug development. Among the compound that has been isolated from plants in recent years include the anticancer agent paclitaxel (Taxol) from the yew tree and the antimalarial agent artemisinin from *Artemisia annua* [1].

1.2. Natural products as anticancer agents

It has long been known that a diet rich in fresh fruits, vegetables, seeds, grains, legumes and antioxidants, and other beneficial compounds may help prevent diseases. The evidences are compelling that healthy diet supplemented with vitamins, antioxidants or other beneficial micronutrients has real influence in reducing cancer incidence and mortalities. It was estimated that one-third of all cancer cases could be prevented by a healthy diet [4, 5].

Although the search for natural compounds against cancers is still ongoing and exhaustive, more than 100 new products have already been developed for cancer therapy. However, the potential discovery of new cancer therapeutics is still enormous because approximately 80% of the rain forest plant species are likely to contain chemicals with anticancer properties, while only a fraction of these plants has been analyzed for their therapeutic properties [6].

There are several compounds from natural products that can directly or indirectly serve to treat cancers. The immune system can be boosted to recognize cancer cells through glutamine, melatonin, parthenolide, resveratrol (from red grape), carotenoids (pigments in vegetables), indole-3-carbinol, vitamin D, emodin, vitamin E, genistein (from red clover and soy products), proanthocyanides (from grape seed and pine bark), flavonoids (from tea family and berry family), and lycopene (from tomatoes) [7]. Other compounds proposed to have anticancer properties are garlic (*Allium sativum*), ginkgo (*Ginkgo biloba*), echinacea (*Echinacea purpurea*), ginseng (*Panax ginseng*), St John's wort (*Hypericum perforatum*), ginger (*Zingiber zerumbet*), kava (*Piper methysticum*) [8] and cabbage, licorice, onions, flax, turmeric, cruciferous vegetables, peppers, brown rice, wheat, and the umbelliferous vegetables such as carrots, celery, and parsley [6].

1.2.1. *Zingiber*

Ginger herb with white, red, or yellow flowers and dark green leaves and thick roots is a set of plants with various medicinal and culinary values found in many parts of the world including Malaysia. Ginger belongs to the genus *Zingiber* representing approximately 141 species under the family Zingiberaceae. The word ginger comes from the Latin Sanskrit word Sringavera, meaning that the rhizomes look like antlers of deer or horns of bull. The underground stems of ginger, which is the rhizomes, are knobby and fleshy, covered in ring-like scars and are used as food and medicine. Among the ginger, species with potential for high medicinal values are *Zingiber officinale* and *Zingiber zerumbet* [8, 9].

1.2.2. *Zingiber zerumbet* (L.) Smith

Zingiber zerumbet (L.) Smith (**Figure 1**) is an edible ginger, native to India and the Malay Peninsula, although it can be found in many countries including Indonesia, China, Bangladesh, Vietnam, Japan, Burma, Nepal, Sri Lanka, Jamaica, and Nigeria. This herbal plant is commonly known as the pinecone, wild ginger, Asian ginger or shampoo ginger. It is known by various names in different countries such as *lempoyang* in Malaysia and Indonesia, *Ghatian* and *Yaiimu* in India, *Jangliadah* in Bangladesh, *Hong qui jiang* in China, *Haeo dam* in Northern Thailand, *Awapuhi* in Hawaii, and *zurunbah* among the Arabians [8]. Generally, the rhizomes and leaves are used for spice, tea, beverages, and medical purposes, while the milky, mucilaginous substance of the pinecones is used as shampoo and natural hair conditioner [9].

Zingiber zerumbet contains several types of phytochemicals and is considered as one of the widely used traditional dietary condiments for cuisines, food, and beverages throughout the Asia, and the essential oil is used as perfume and toilet article. In traditional oriental medicine, the oil is used for a variety of digestive conditions [10]. The extract of the rhizome has been extensively studied for its antimicrobial, anticonvulsant, antipyretic, analgesic, antiulcer, antioxidant, antitumor, anticancer, antispasmodic, anti-inflammatory, antinociceptive, anticoagulant, antidiabetic, antihyperlipidemic and antiobesogenic, anti-allergenic, anti-platelet aggregation, and hepatoprotective activities. Additional studies

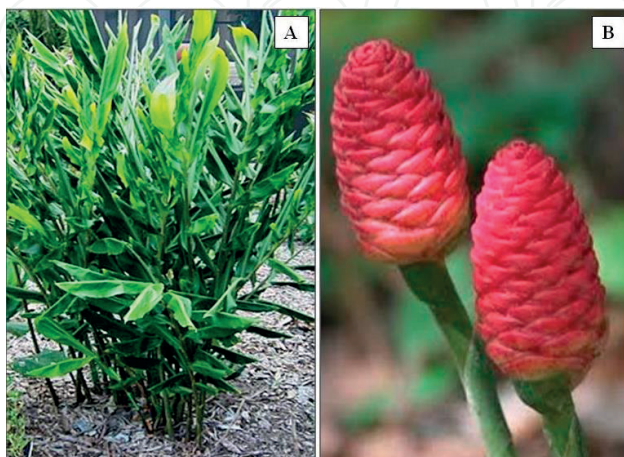


Figure 1. *Zingiber zerumbet* (A) tree and (B) inflorescence.

had showed that rhizome consumption can lower blood cholesterol levels by reducing cholesterol absorption in the blood and liver, making this extract useful for treatment of heart diseases [11–13].

1.2.3. Ginger oil

Ginger oil is obtained from unpeeled or dried, ground-up root (rhizome) of *Zingiber zerumbet* by steam distillation. Ginger oil can vary in color from pale yellow to a dark amber, and the viscosity ranges from medium to watery. It has a strong spicy odor, sharp, warm and with a hint of lemon and pepper, and smells of actual ginger. The taste of ginger oil is peculiar and pungent [14].

1.2.4. Zerumbone

Zerumbone (ZER) was first isolated in 1960 from the essential volatile oil of rhizomes of *Zingiber zerumbet*, while its structure was first determined in 1965 and later characterized by NMR and X-ray. Zerumbone (**Figure 2**) is a sesquiterpene phytochemical compound isolated from *Zingiber zerumbet* (L.) smith or *Zingiber aromaticum*. It contains three double bonds, two conjugated and one isolated, as well as a conjugated carbonyl group in 11-member ring structure [16, 17]. Among parts of the plant richest in ZER are rhizomes followed by the leaves [18, 19]. Zerumbone is also the major compound (59%) in the essential oil from *Zingiber zerumbet* [20].

1.3. General medicinal properties of zerumbone

Several biological activities of ZER have been reported both *in vivo* and *in vitro*. These studies have found ZER to possess antitumor, anti-inflammatory, antioxidant, antimicrobial, antinociceptive, antiatherosclerosis, hepatoprotective, antiplatelet aggregation, and immunomodulatory activities at different doses and concentrations [21].

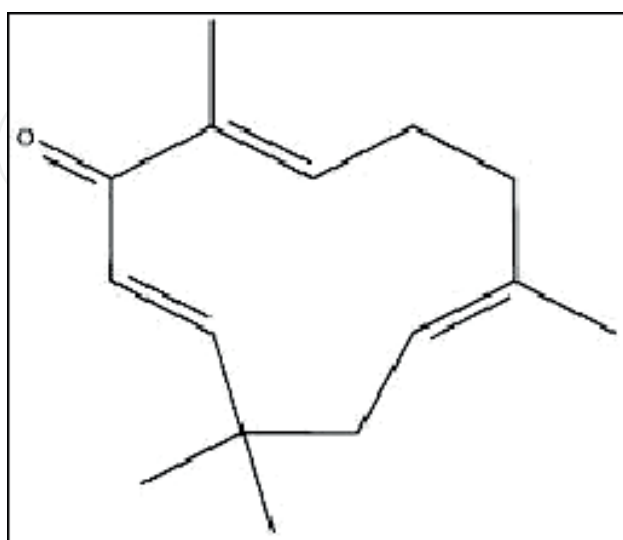


Figure 2. Chemical structure of zerumbone [15].

1.4. Carrier systems for drug delivery

Generally, the number of drugs and drug candidates is steadily increasing over the last 2 decades. A number of these drugs have poor water solubility, which consequently cause poor oral bioavailability and delivery. Drug of poor bioavailability will not be readily absorbed from the gastrointestinal tract into circulation and would not reach the site of action. However, solubilization of poorly soluble drugs is limited by drug properties, chemistry, molecular size, and selective solubility in certain organic media [22]. For several years approaches to increase drug solubility by solubilization with surfactants, complex formation (cyclodextrins and macromolecules), microemulsions, and micronization of drug powders to increase the surface area and stability has not been very successful because the dissolution velocity of these drug was insufficient to overcome the lack of bioavailability to meet biopharmaceutical specification [23]. Therefore, there is a desperate need to develop innovative pharmaceutical carriers and delivery systems that overcome these drawbacks. Generally, carrier schemes for drug delivery should be toxicity-free, possess sufficient drug loading capacity, and have tissue targeting and controlled release characteristics. The carriers should also afford chemical and physical stability to incorporated drug. To achieve their commercial potentials, these carrier and delivery systems should be feasible for production scaling-up at reasonable costs [24].

1.5. Colloidal carrier system

Colloidal drug carrier systems (**Figure 3**) have received great attention as potential drug delivery system because they offer many advantages as drug delivery vehicles including capability of increasing dissolution velocity that also increases bioavailability and solubility saturation. This can be achieved by reducing the size of the particle that increases surface area while increasing dissolution velocity. Thus, suitable nanoparticles can be employed as delivery systems with solid colloidal particle size ranging from 1 to 1000 nm [25].

Colloids consist of least two components; one dispersed in the other as fine particles in any state of matter. As pharmaceutical carriers, colloidal drug delivery systems can be classed into polymer systems (micelles, dendrimers, etc.), self-assembled lipid systems (liposomes, emulsions, SLN, NLC, etc.), drug nanoparticle systems, and pro-colloidal systems (self-emulsifying oral delivery systems and liquid crystalline systems) [23]. Lipids are physiologically natural occurring compounds that are well tolerated, usually nontoxic or degradable to nontoxic residues. Thus, the lipid-based nanoparticles provide an advantage over other types of carrier systems. Liposomes and micelles are among the first colloidal drug carriers developed to overcome the possibilities of water-insoluble drug formulations [26]. They are naturally derived phospholipids and surfactant vesicles that can be filled with various drugs [27]. Liposomes and micelles are rapidly degraded by the pH of the stomach, intestinal enzymes, and bile salts after oral administration but have restricted physical and chemical stability during storage. These particles characteristically cause fast release of the drug while not so stable over extended period of storage. The liposomes and micelles also leave behind residues of the organic solvents and cause some degrees of toxicity to normal tissues. These characteristics make these colloidal carriers not optimal as a pharmaceutical carrier system.

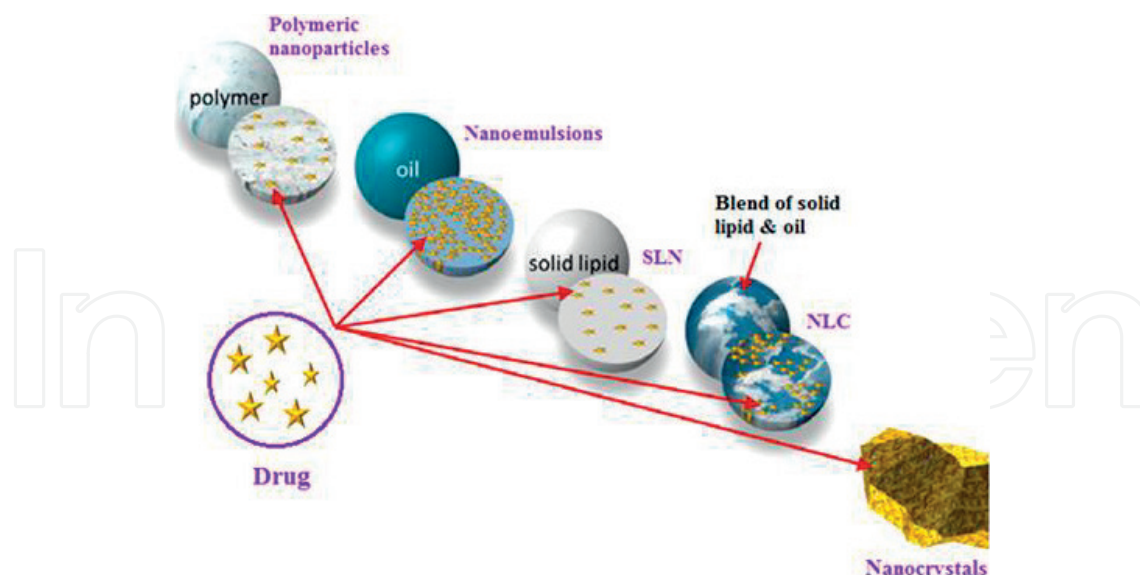


Figure 3. Various types of nanoparticles as drug delivery system. SLN—solid lipid nanoparticle and NLC—nanostructured lipid carrier. (<http://www.pharmatutor.org/articles/nanotechnology-nanocrystal>, 2013).

1.6. Nanoparticles

Solid lipid nanoparticle (SLN) (**Figure 4**) is also a colloidal drug carrier system developed as an alternative system to the existing traditional carrier systems [28]. Although SLN have numerous advantages including targeted drug delivery and increased stability of incorporated drug, they are still fraught with limitations. The matrix of SLN is highly ordered crystalline lipid structure leaving very little space for incorporation of drug molecules, thus limiting the loading capacity. The net effect of these properties is expulsion of incorporated drug during storage. To overcome these limitations, a second generation lipid nanoparticle, the nanostructured lipid carrier (NLC) was introduced [29]. Nanostructured lipid carrier is a novel lipid nanoparticle, which in contrast to SLN consists of a mixture of solid and liquid lipids, in fine proportions. This formulation of NLC prevents the formation of perfect crystals and minimizes the drug expulsion phenomenon during storage [30]. With the introduction of NLC, lipid colloid carriers began to gain new life as a potential drug carrier and delivery system [29].

In last couple of years, NLC has attracted great attention as an alternate carrier for the pharmaceutical for anticancer drugs [24]. The NLC contains liquid lipids with different fatty acid C-chains responsible for producing the less-organized crystalline structure, providing better and higher drug loading capacity accommodation [31]. Several methods have been used to prepare the lipid nanoparticles of different size, surface characteristic, and stability. The preparation of stable NLC of high surface area is based on three principles, namely precipitation, milling, and high pressure homogenization [22]. In the precipitation phase, the drug is dissolved in a solvent and subsequently added to a nanosolvent resulting in the precipitation of finely dispersed drug nanoparticles [25]. In the milling method, the dimension of particles is achieved by using different sizes of bead, ball mills or a pearl mill that consisting of ceramics, stainless steel, glass or highly cross linked polystyrene resin coated as milling media. The high pressure homogenization (HPH) generates small nanoparticle under pressure. Surfactants are required to stabilize the particle at the desired size. Lipid nanoparticles can also be produced by either hot or cold HPH technique. Other less common methods include spray drying,

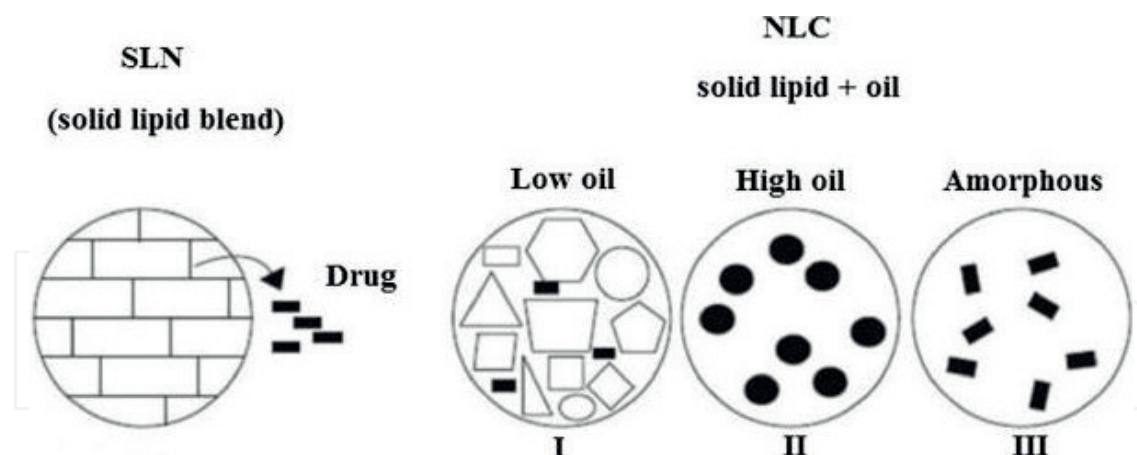


Figure 4. Solid lipid nanoparticle and nanostructured lipid carriers. I—highly imperfect matrix, II—multiple oil/fat/water type, and III—noncrystalline nanostructured nanoparticle [24].

ultrasonication, solvent evaporation, film ultrasound dispersion, microemulsion based, and supercritical fluid methods [25].

1.7. Nanostructured lipid carriers

Nanostructured lipid carriers are fine blends between solid and liquid lipids stabilized by the introduction of surfactants. Three different approaches have been developed to optimize the structure of NLC. First, imperfect type or type I NLC is prepared by blending spatially different lipid types (solid and oil) to create distance between the fatty acid chains of the glycerides and imperfections in the crystal. This procedure offers more space for the accommodation of drug molecules and amorphous clusters of drugs, thus higher drug loading in the NLC. At the final stage, solid particles are produced by crystallization of liquid lipid particles (nanoemulsions) at room temperature from the cooled molten state. Basically, drug solubility is higher in liquid lipids than in solid lipids, and thus particles produced with high content of liquid lipids can load more drug [32]. Multiple type or type II NLC is prepared by mixing high liquid lipid, solid lipid, water, and drug. The high oil concentrations produce miscibility gap between solid lipids and liquid lipids during the cooling phase leading to phase separation and consequently precipitation of tiny oily nanocompartments. Finally, amorphous type or type III or multiple oil/fat/water type NLC is prepared by mixing solid lipids while in amorphous state. Solid lipid particle crystallization that can occur upon cooling is prevented by adding special lipids such as hydroxyoctacosanyl-hydroxystearate and isopropyl myristate [25, 32].

1.8. Characterization of nanostructured lipid carriers

Characterization of NLC is essential to determine the properties of the nanoparticle. Among the techniques employed to characterize nanoparticles include image analysis which includes light microscope, scanning electron microscope (SEM), transmission electron microscope (TEM), and atomic force microscope (AFM) to characterize and determine particle size and shape. Nuclear magnetic resonance (NMR) is used to determine particle size and qualitative nature of nanoparticle. Other characteristics of nanoparticles of concern are zeta potential (ZP), which characterizes ionization properties that dictates the agglomeration behavior of nanoparticles. Polydispersity index (PDI) is a measure of distribution of molecular mass in a given

polymer sample. It is a measure of particle size distribution. The PDI values are always greater than 1; however, as the size becomes more uniform, the PDI approaches 1. The ZP, PDI, and particle can be determined using a Zetasizer. The efficiency of nanoparticles as a drug carrier system can be partially determined by the entrapment efficiency (EE) and drug loading (DL) capacity. Entrapment efficiency is the ratio of weight of drug entrapped in a carrier system to the total drug added, while DL is the ratio of drug to the weight of the total carrier system. The EE and DL can be determined by high performance liquid chromatography (HPLC) technique, which at the same time can be used to determine the content of a substance and/or its chemical stability. It is optimal for a drug delivery system to exhibit sustained release characteristics. This feature of drug-loaded nanoparticles can be analyzed using the Franz Diffusion Cell (FDC), which determines the rate of drug release from lipid particles. Thermal stability is another important feature of a drug carrier and nanoparticle delivery systems. This is essential because the preparation of these particles is done under high temperatures. The differential scanning calorimetry (DSC) is used to determine the physical and energetic properties of a substance as a function of temperature. The X-ray diffractometer was developed to measure the geometric scattering radiation from crystal planes within nanoparticle dispersion for assessing the degree of crystallinity using wide-angle X-ray diffraction (WXR) [33, 34].

1.9. Nanoparticles in parenteral applications

In disease therapy, nanoparticles can be administered via several routes of administration, that is, parenteral, oral, intraocular, rectal, nasal, transdermal, or pulmonary inhalation [25, 35]. Thus, the understanding of the nature of targets and their interaction of the nanoparticles in a biological environment is imperative in the design of carrier systems [33]. Nanoparticles are large enough to be removed from circulation after intravenous injection by the macrophages through phagocytosis. Thus, this rapid removal of colloidal particles by the free circulating macrophages is a major obstacle of tissue targeting of drug-loaded nanoparticles. Similarly, fixed macrophages in tissue can also be phagocytose carrier drugs. Particles smaller than 7 μm are normally trapped in the small pulmonary vessels, while larger particles will pass through capillary beds of lungs to liver and spleen, which are then engulfed by the fixed macrophages. Consequently, these organs will be the primary deposition sites for small nanoparticles [32]. The size, surface properties of carrier, and the total amount of serum protein adsorbed on the surface of nanoparticle are the most important factors affecting the macrophage uptake process of drug carrier. The rate of clearance of the drug carriers is approximately proportional to the amount of serum protein adsorbed on their surfaces. Hydrophobic particles will be removed from the circulation more rapidly than hydrophilic particles. Thus, to prolong circulation time, the drug carrier should be formulated with little to no serum adsorption. Currently, among the challenges is the design and formulation of colloidal carriers with prolonged distribution in the body is to find means to delay clearance from the body by avoiding the macrophages of the monocyte-phagocytic system [25].

1.10. Nanoparticles for cancer therapy

The development of nanotechnology is exponential and touted to be the technology that could revolutionize how drugs are delivered. Transfer of materials into the nanodimensions changes

their physical properties but not their biological activities, and this phenomenon is used in pharmaceuticals to develop new innovative formulations for poorly soluble drugs [36]. The use of nanotechnology in cancer treatment offers some exciting possibilities, including tissue targeting and destruction of cancerous cells and tumors with minimal toxicity to the healthy tissue and organs. If well designed, the formulations may detect and eliminate cancer cells early before they form tumors [37]. The small size of nanoparticles endows them with properties that allow them to preferentially accumulate at tumor sites and when used in association with magnetic resonance imaging (MRI) can produce exceptional images of the tumors. Another property of nanoparticles is the high surface area to volume ratio that allows many functional groups to be attached, for example, groups that can seek out and bind to tumor cells [38].

2. Conclusion

Cancer nanotherapeutics is rapidly progressing and is being implemented to overcome limitations of conventional drug delivery systems. Early clinical results suggest that nanoparticle therapeutics shows enhanced efficacy, while reducing side effects. The major role of nanoparticle in drug delivery is to increase the dissolution velocity by reduction size and increasing surface area and bioavailability. Nanoparticle can carry loaded drugs to cancer cells selectively through the unique pathophysiology of tumors, such as enhanced permeability and retention of drugs in the tumor microenvironment.

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