

# Cancer, Natural Products and Nanodrug Delivery Systems

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**Abstract:** As an offshoot of nanotechnology, nanomedicine has made great impact in the field of pharmaceutical and biomedical sciences by achieving breakthroughs in therapeutics and diagnostics of diseases in living organisms. One of the promising breakthroughs is the application of natural product-based nanoformulations for the treatment of various human diseases, such as cancer. Principally, the nanoparticle-based drug delivery system (NDDS) aims to overcome the limitations of conventional drug delivery system. NDDS improves the *in vivo* pharmacological and therapeutic properties of the poorly soluble drugs by dissolving, encapsulating, absorbing and/or attaching the drugs with the matrices of the nanoparticles. The nanoparticles that act as drug reservoirs also aim to control the drug release, enhance the drug uptake by targeted delivery and protect the drug against enzymatic degradation. This review presents a summary of the integration of nanotechnology and phytotherapy to achieve an improved pharmacological response and better clinical outcome in patients undergoing chemotherapy.

**Keywords:** nanomedicine; chemotherapy; natural product; drug delivery; nanoparticles

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## INTRODUCTION

Cancer remains as one of the leading causes of mortality globally, irrespective of the advent of current available forms of cancer treatment. In 2018, cancer has accounted for an estimated of 9.6 million deaths worldwide<sup>[1]</sup>. The current therapeutic modalities, such as chemotherapy and radiotherapy, are associated with limitations, including damaging to proliferating healthy tissues, systemic toxicity, chronic side effects and emergence of drug resistance within tumor cells. Hence, there is always a continuous need of more effective strategies for the treatment of different human malignancies.

Throughout the history of mankind, natural products have played a pivotal role in the treatment of various diseases. Natural products derived from plants, animals and microorganisms represent the prolific bioresources for pharmacologically active compounds, including as chemotherapeutic agents<sup>[2-12]</sup>. These natural products have been extensively studied for the prevention and treatment of cancer, such as paclitaxel, vincristine, camptothecin and resveratrol<sup>[13]</sup>. Although they have been demonstrated to possess strong therapeutic value, the clinical application

of these promising natural product derived compounds is severely hampered by their poor solubility and bioavailability<sup>[14]</sup>.

As an offshoot of nanotechnology, nanomedicine has made great impact in the field of pharmaceutical and biomedical sciences by achieving breakthroughs in therapeutics and diagnostics of diseases in living organisms. One of the promising breakthroughs is the use of nanoparticles in the development of drug delivery system to improve the treatment of various diseases, including cancer<sup>[15]</sup>. Principally, the nanoparticle-based drug delivery system (NDDS) aims to improve the *in vivo* pharmacological and therapeutic properties of the poorly soluble drugs by dissolving, encapsulating, absorbing and/or attaching the drugs with the matrices of the nanoparticles. The nanoparticles that act as drug reservoirs also aim to control the drug release, enhance the drug uptake by targeted delivery and protect the drug against enzymatic degradation. In 2005, the National Cancer Institute (NCI) has launched the Alliance for Nanotechnology in Cancer due to the emerging of nanomedicine and their potential applications in

cancer research<sup>[16]</sup>. Under this approach, nanoparticle-based drug delivery system has been approved as one of the effective strategies to overcome the limitations of conventional chemotherapy with numerous nanoparticle-based drugs and delivery system that are in clinical use. In this review, we aim to critically consolidate the advent of nanotechnology in the context of chemotherapeutic drug delivery. This review also presents the examples of the extensively studied natural product-derived compounds using nanotechnology, including doxorubicin, paclitaxel and vincristine.

## BRIEF OVERVIEW OF CANCER

Cancer is a collection of genetic diseases characterized by the uncontrolled cell growth as a result of dysregulated processes of cell division and cell death. Cancer cells are abnormal cells which lose their ability to undergo apoptosis (the programmed cell death) and uncontrollably proliferate, subsequently leading to formation of malignant tumour that invades to adjacent tissues<sup>[16]</sup>. The formation of tumour (tumourigenesis) involves a complex multistep process (tumour initiation, tumour promotion and tumour progression) that transforms a normal cell into a malignant one due to DNA mutation. In 2011, “the hallmarks of cancer” have been revised, explaining the defect mechanisms of malignant cells that deviate from normal cellular functions (Figure 1)<sup>[17]</sup>.



Figure 1. The ten hallmarks of cancer<sup>[17]</sup>.

These cancer hallmarks are the common traits of tumour cells with their capabilities to alternate the cell growth (sustaining proliferative signalling and evading growth suppressors), to evade apoptosis and cell cycle (resisting cell death and enabling replicative immortality), to modify cellular metabolism (deregulating cellular energetic), to destruct immunological function, to induce angiogenesis, invasion and metastasis. Additionally, the genomic instability<sup>[18-22]</sup> and inflammation by immune cells facilitate the tumourigenesis<sup>[17]</sup>.

## APOPTOSIS AND CANCER

One of the prominent hallmarks of cancer is the

ability to resist cell death<sup>[17]</sup>. Cell death is a fundamental programme that happens for two purposes; under defence mechanism when the cells received stressful stimuli or under homeostasis mechanism to remove damaged or aged cells for maintaining cell population<sup>[23, 24]</sup>. The cell death could occur by either necrosis or apoptosis, depending on the response of the cell to the stimuli<sup>[25]</sup>.

Necrosis is an “accident” or premature cell death that occurs when the cells encountered irreversible stimuli such as infectious agents, hypoxia, heat and radiation<sup>[26]</sup>. The necrotic cells experience rupture in the plasma membrane and organelles due to the swelling of cytoplasm. The cytoplasmic contents are then released to the extracellular space and triggered an inflammatory response<sup>[27]</sup>.

In contrast, apoptosis is a “suicide” or programmed cell death that occurs under some physiological conditions to maintain homeostasis<sup>[28]</sup>. Aged and damaged cells that may interfere with body function are removed from the system<sup>[29]</sup>. Apoptotic cells experience the blebbing of plasma membrane, cell shrinkage, DNA fragmentation and activation of specific proteases (caspases). As different from necrosis, the apoptotic process does not trigger the inflammatory response as the apoptotic cell externalises the phosphatidylserine at the outer leaflet of plasma membrane to be recognised and engulfed by phagocytes<sup>[30,31]</sup>.

Tumour initiation (hyperproliferation of cell) happens when apoptosis fails to eliminate the genetic mutated cells<sup>[32]</sup>Ryia-Illani Mohd. These mutated cells proliferate uncontrollably by evading apoptosis via several mechanisms. One of the common mechanisms is the loss of function of *TP53* tumour suppressor gene<sup>[17]</sup>. *TP53* tumour suppressor gene encodes the p53 protein which is responsible to transcript more than 125 genes coordinating the repairing of DNA, cell cycle and apoptosis. The mutation of *TP53* gene has been identified as a common molecular characteristic in human cancer<sup>[33]</sup>. Therefore, *TP53* has become a potential target in cancer treatment with the aim to restore the transcription function<sup>[34]</sup>.

Apoptosis is executed via two downstream signalling pathways: intrinsic and extrinsic pathways, depending on the source of the stimuli (Figure 2)<sup>[35]</sup>. The intrinsic pathway receives the intracellular death signals from non-receptor-mediated stimuli and initiates the events in mitochondria<sup>[24]</sup>. The up-regulation of pro-apoptotic proteins (Bax, Bad and Bim) or/and down-regulation of anti-apoptotic proteins (Bcl-2, Bcl-xL and Bag) stimulate the release of cytochrome c from mitochondria, leading to the formation of apoptosome in the cytosol. The apoptosome then initiates a cascade of proteolysis with the effector caspases (caspase-3 and -7) that lead to the execution of apoptosis<sup>[36]</sup>.

On the other hand, extrinsic pathway receives extracellular death signals from transmembrane death receptors such as tumour necrosis factor (TNF) receptor and Fas receptors after binding with their homologous ligands (TNF- $\alpha$  and FasL). Activation of these death receptors results in the activation of Fas-associated death domain protein (FADD) and caspase-8 that further initiates the effector caspases (caspase-3 and -7) and triggers apoptosis<sup>[37, 38]</sup>.

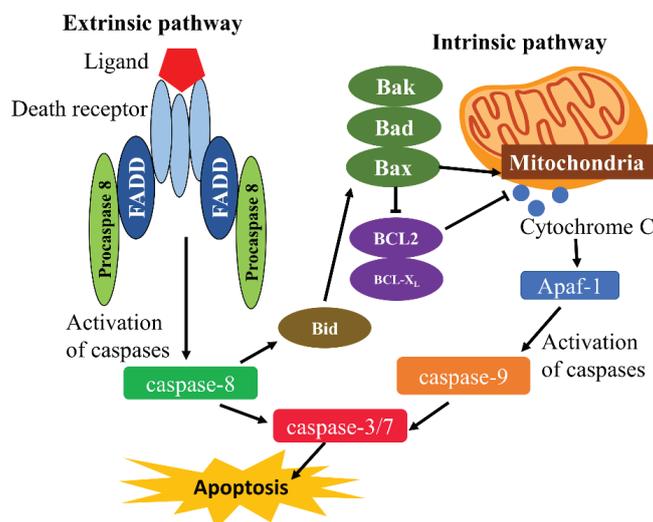


Figure 2. The intrinsic and extrinsic pathways of apoptosis<sup>[35]</sup>.

## Angiogenesis and Cancer

Another hallmark of cancer is the induction of angiogenesis<sup>[17]</sup>. Angiogenesis is the formation of new blood capillaries from existing blood vessels<sup>[39]</sup>. Formation of new capillaries in the tumour enables the tumour cells to obtain nutrients and oxygen and to remove the metabolic waste and carbon dioxide. This has promoted the tumour growth and metastasis of tumour cells to other organs<sup>[17,40]</sup>. Vascular endothelial growth factor (VEGF) family members such as VEGF A and B proteins are the key components to induce angiogenesis. In response to hypoxia, the level of hypoxia inducible factor-1  $\alpha$  (HIF-1 $\alpha$ ) promotes the expression of these pro-angiogenic VEGFs in tumour<sup>[41]</sup>. The VEGFs then bind to their respective receptors on the endothelial cells in the extracellular matrix, causing the differentiation of endothelial cells to form new capillaries<sup>[42]</sup>. Therefore, VEGF has become the therapeutic target to control the tumour growth, angiogenesis and metastasis<sup>[41,43]</sup>.

## Metastasis and Cancer

Activation of invasion and metastasis is one of the characteristics of malignant cancer<sup>[17]</sup>. Metastasis is defined as the spread or development of cancer in other distinct organs from the primary tumour through blood and/or lymphatic vessels<sup>[44]</sup>. It is always related to poor prognosis as it is the leading cause of cancer death<sup>[45]</sup>. For tumour cells to pass through the tissue barriers, they have to develop the ability to break through the extracellular matrix (ECM)<sup>[46]</sup>. One of the proteolytic enzymes that are responsible to degrade

ECM is the matrix metalloproteinases (MMPs). ECM metalloprotease inducers (EMMPRIN) are produced on the membrane of the tumour cells to activate MMPs including the MMP-2 (72-kDa Gelatinase A) and MMP-9 (92-kDa Gelatinase A)<sup>[47]</sup>.

## NATURAL PRODUCTS AS A SOURCE OF CHEMOTHERAPEUTIC AGENTS

Natural products are defined as the compounds that are produced from nature such as plants, microorganisms and animals as a result of nutritional needs and evolution to adapt the environmental challenges<sup>[48-62]</sup>. Historically, plants have been extensively documented in traditional medical systems such as traditional Chinese medicine, Indian Ayurvedic system and Egyptian “Ebers Papyrus” to promote health and cure diseases<sup>[63]</sup>. Nowadays, plants have become an important source for discovery of bioactive compounds (phytochemicals) with promising therapeutic activities such as anti-cancer, anti-inflammatory and anti-bacterial effects<sup>[13,64-75]</sup>.

Majority of the marketed chemotherapeutic agents were isolated and derived from medicinal plants due to the advantages of readily available and cost effective<sup>[76]</sup>. The well-known examples of plant-derived chemotherapeutic compounds are paclitaxel from *Taxus brevifolia*<sup>[77]</sup>, camptothecin from *Camptotheca acuminata*<sup>[78]</sup>, vinblastin and vincristine from *Catharanthus roseus*<sup>[79]</sup>. These phytochemicals can be further classified into alkaloids, flavonoids, taxanes, lignans, stilbenes and more<sup>[76]</sup>. **Table 1** summarises some of the potential and clinically approved plant-derived chemotherapeutic compounds with their mechanisms of action.

Table 1. Potential and clinically approved plant-derived chemotherapeutic compounds with their mechanisms of action

Phytochemical	Plant name and part	Mechanism of action and type of cancer	Reference
Camptothecin	<i>Camptotheca acuminata</i>	- DNA topoisomerase I inhibitor in glioblastoma, ovarian, lung and colorectal cancers	[78]
- Synthetic derivatives: topotecan and irinotecan	(bark and stem)		
Vinca alkaloids (vincristine and vinblastine)	<i>Catharanthus roseus</i> (leaves and bark)	- Microtubules acting agent that arrests cell cycle in leukemia, breast, lung and liver cancers	[79,80]
- Synthetic derivatives: vinorelbine, vindesine, and vinorelbine			

Colchicine  - Synthetic derivatives: colchicinamide, deacetylcolchicine	<i>Colchicum autumnale</i> (leaves)	- Arrest cell cycle by binding to tubulin in melanoma, colorectal and breast cancers [81,82]
Pomiferin	<i>Maclura pomifera</i>  (fruits and flowers)	- Inhibit histone deacetylase and cause oxidative DNA damage in colorectal cancer [83]
Paclitaxel  - Synthetic derivative: docetaxel	<i>Taxus brevifolia</i>  (barks and leaves)	- Microtubules acting agent that binds to $\beta$ -tubulin and arrests cell cycle in breast, ovarian and prostate cancers [77,84]
Podophyllotoxin  - Synthetic derivatives: etoposide and teniposide	<i>Podophyllum peltatum</i>  (leaves)	- Inhibit microtubule polymerization and arrest cell cycle at G2/M phase [85,86]  - Induce apoptosis via modulation of intrinsic and extrinsic pathways in non-small cell lung carcinoma
Resveratrol	<i>Veratrum grandiflorum</i>  (leaves)	- Inhibit angiogenesis and induce apoptosis via modulation of VEGF, p53, Bax, Bcl-2, cytokines, and COX-2 proteins in breast, liver, prostate, lung and colorectal cancers [87,88]
Thymoquinone	<i>Nigella sativa</i> (seed oil)	- Induce apoptosis via modulation of intrinsic pathway in breast cancer [89]
Geniposide	<i>Gardenia jasminoides</i> (Fruit)	- Antioxidant and anti-inflammatory via induction of Nrf2 and GPx [90]

### NANOTECHNOLOGY IN DRUG DELIVERY: NANOMEDICINE

The word “Nano” comes from the Greek “*nannos*” (dwarf or a very short man) that refers to the prefix of one-billionth of a meter (a factor of  $10^{-9}$ )<sup>[91]</sup>. According to the National Nanotechnology Initiative (NNI), nanotechnology is defined as “the knowledge and manipulation of matter within nanometer scale (1–100 nm) that comprises multidisciplinary fields of nanoscale science, engineering and technology”. Owing to the abilities to shape, process and create things at nanoscale, nanotechnology has been addressed as the next “Industrial Revolution” that offers tremendous advances to human being in the application of communications, chemistry, engineering, medicine and robotics<sup>[91,92]</sup>.

One of the most active applications of nanotechnology is nanomedicine<sup>[93]</sup>. Nanomedicine is defined as “the

application of nanotechnology in the field of medicine”<sup>[94]</sup>. With the utilisation of nanoparticles, nanotechnology has brought positive impact to human health in diagnosis, prevention and treatment of diseases<sup>[95]</sup>. It involves the development of nanomaterials and nanodevices for the applications of drug delivery, *in vivo* diagnosis, implants and nanotheranostics<sup>[96]</sup>. Nowadays, various types of material have emerged as useful nanomaterials for the development of drug delivery system. The nanoparticles can take various shapes and sizes with distinct properties depending on the types of nanomaterials used. Generally, nanoparticle-based drug delivery systems can be categorized based on biological-origin materials (such as phospholipids, dextran, lipids, chitosan, and lactic acid) or inorganic materials (such as polymers, carbon, silica and metals)<sup>[97,98]</sup>. The family of nanoparticles, including polymeric nanoparticles, lipid nanoparticles and inorganic nanoparticles, is illustrated in Figure 3<sup>[99]</sup>.

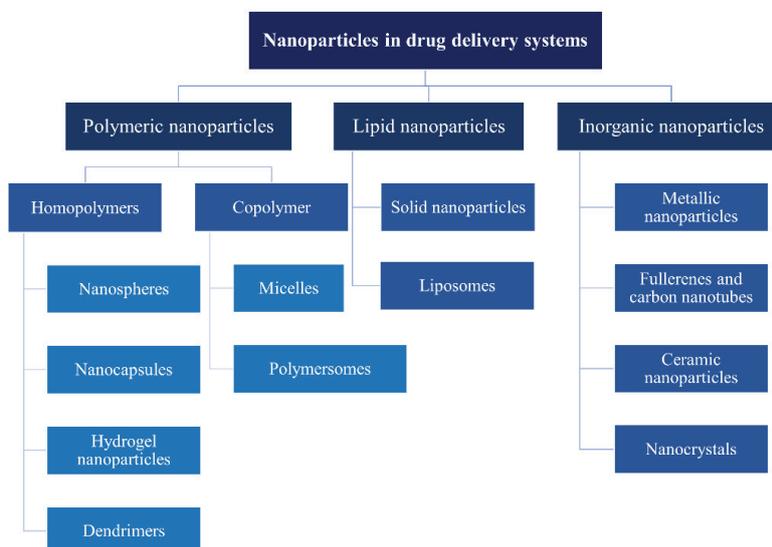


Figure 3. Family of nanoparticles in drug delivery systems.

Drug delivery is defined as “a process of delivering a pharmaceutical agent for pharmacological reactions”<sup>[100]</sup>. An ideal drug carrier used in the drug delivery system should possess the ability to transport the optimum dose of pharmaceutical agent to the desired site without causing adverse side effects in other tissues due to unwanted accumulation<sup>[101]</sup>. Besides, the intentions of drug carriers are to protect the therapeutic agents from degradation by gastrointestinal enzymes, to improve the bioavailability of hydrophobic or lipophilic therapeutic agents and to facilitate controlled release of drug<sup>[102–106]</sup>. On top of these criteria, nanoparticles have been developed as the novel drug delivery system that provide extra advantages of low possibility of rapid clearance from the body through extravasation or prevention from phagocytosis by macrophage due to their nanometer size<sup>[107,108]</sup>.

### Limitations of Conventional Delivery of Chemotherapeutic Agents

Chemotherapy is the most common therapeutic approach for breast cancer. The highly-cytotoxic chemotherapeutic agents are directly administered into the blood circulating system by intravenous or oral route to kill rapidly-dividing cells<sup>[110]</sup>. However, this conventional drug delivery system encounters some drawbacks as follows:

- A Non-specificity of chemotherapeutic agents:** The random distribution and non-specific targeting of chemotherapeutic agents in the body system have caused unwanted accumulation and toxicity to other normal cells that divide rapidly such as bone marrow, hair follicle and digestive tract cells<sup>[111]</sup>. The most common adverse effects of chemotherapy are anaemia, alopecia, nausea, vomiting and acute cholinergic gastrointestinal effects<sup>[112]</sup>.
- B Poor pharmacokinetics via oral administration:** Cancer is considered as chronic disease that requires long term frequent treatment. Therefore, oral route of drug administration has been the most preferred choice due to the reasons of patient’s convenience, compliance, lower cost and painless<sup>[113]</sup>. Nevertheless, the desired therapeutic dose needed for maximum therapeutic effect is hard to achieve via oral administration of active drugs due to the enzymatic and hydrolytic degradation in the gastro-intestinal fluids, low cell uptake in the gastro-intestinal tract, first-pass hepatic metabolism, susceptibility to efflux transport and short biological half-life<sup>[114, 115]</sup>.
- C Poor aqueous solubility:** Conventional delivery of chemotherapeutic agents remains a challenge as more than 40% of the potential anti-cancer compounds are hydrophobic or lipophilic. The insolubility of these drugs in water becomes an issue as they could not achieve the desired concentration in the systemic circulation. Therefore, various methods have been applied to improve the drug solubility such as drug carrier, chemical/physical modification of drugs, use of surfactant and salt formation<sup>[114]</sup>.

## APPLICATION OF NOVEL DRUG DELIVERY SYSTEM IN CANCER THERAPY

Nanotechnology has appeared as an attractive approach for solving the drawbacks of conventional drug delivery system of chemotherapy. In principle, the potential or existing chemotherapeutic agents are conjugated or encapsulated in the nanoparticles in order to improve their pharmacokinetics and bioavailability<sup>[116,117]</sup>. As compared to discovery of new chemotherapeutic agents, the development of this novel drug delivery system only utilized half of the time (6–8 years) and 20% of the cost (\$50–\$60 million) to be clinically approved and marketed<sup>[111]</sup>.

In 2005, the National Cancer Institute (NCI) has launched the Alliance for Nanotechnology in Cancer due to the emerging of nanomedicine and their potential applications in cancer research. Under this approach, nanoparticle-based drug delivery system has been approved as one of the promising strategies to overcome the limitations of conventional chemotherapy with numerous nanoparticle-based drugs and delivery system that are in clinical use.

An effective chemotherapeutic drug delivery to a solid tumour involves five steps which are circulation in blood, accumulation and penetration in the tumour, internalization by cancerous cell and drug release (CAPIR)<sup>[118]</sup> (Figure 4).

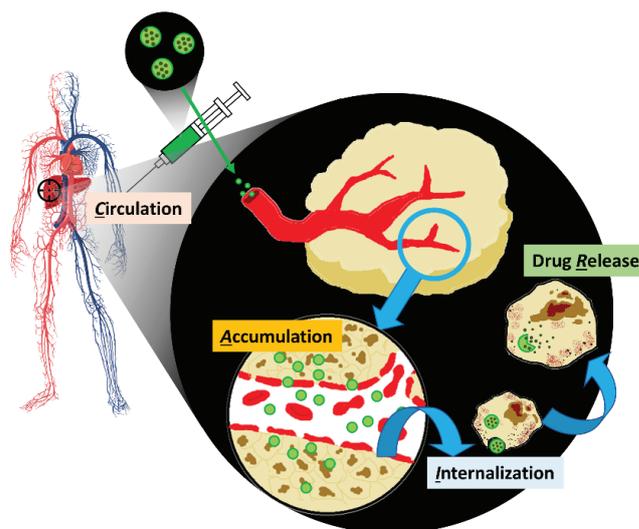


Figure 4. The CAPIR cascade of chemotherapeutic drug delivery<sup>[118]</sup>.

The overall therapeutic efficiency of chemotherapeutic drugs is improved by nanoparticle-based drug delivery system by its abilities of accumulation and penetration in tumour, which could be achieved by either passive or active targeting (Figure 5)<sup>[119]</sup>.

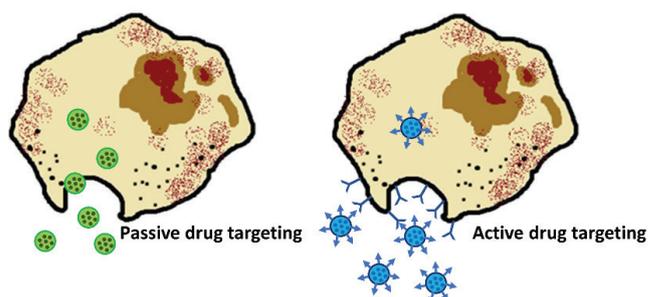


Figure 5. Targeted delivery system by nanoparticles<sup>[119]</sup>.

In passive targeting, the circulating nanoparticles could passively extravasate from blood vessels and accumulate in the tumour via enhanced permeability and retention (EPR) effect. This EPR effect could only be achieved in tumour due to its unique characteristics of leaky blood vasculature and poor lymphatic drainage<sup>[120]</sup>. The normal blood vessels are endowed with tight junctions that could allow molecules less than 10 nm to permeate; meanwhile, the fast growing blood vessels that surround the tumour are highly disorganized and dilated due to the defective smooth muscle and enlarged gap junctions, allowing molecules less than 600 nm to permeate<sup>[121,122]</sup>. Furthermore, the tumour possesses poor lymphatic system that further enhances the entrapment of nanoparticles in the tumour<sup>[123]</sup>.

On the other hand, active targeting can be achieved by attaching the ligands (proteins or antibodies) on the surface of nanoparticles that can interact with specific over-expressed receptors on the tumour<sup>[123,124]</sup>. In principle, this mechanism allows the nanoparticles to identify and recognise cancerous cells, thus minimising the unwanted systemic exposure of chemotherapeutics to

other tissue<sup>[123]</sup>. Table 2 shows some examples of clinically approved nanomedicine for cancer chemotherapy<sup>[109,125]</sup>.

## CONCLUSION

Natural products have been showing impressive potentials as chemotherapeutic agents for cancer treatment, but their success in clinical trial has been limited as they have low solubility and bioavailability. The era of nanomedicine in cancer therapeutics has promisingly overcome the challenges hampering conventional therapy regimes hurdled by barriers of low solubility and physiological stability, poor bioavailability and specificity and high toxicity. Nanotechnology has revolutionized current cancer therapeutic modalities with the introduction of nano-drug delivery systems which are more efficient and less toxic as well as enhanced specificity to target tumor cells. The present *in vitro* and *in vivo* results pose a promising picture, but much more efforts are required from basic molecular aspects to preclinical and clinical trials before advancing more clinical use of nanoformulations in cancer chemotherapy.

**Table 2.** Clinically approved nanomedicine for cancer treatment<sup>[109,125]</sup>

Nanoparticle	Trade name	Description	Type of cancer	Manufacturer
Liposome	Doxil®	- Doxorubicin encapsulated in PEGylated liposomes - Reduced toxicity of doxorubicin	Ovarian and breast cancer	Orthobiotech, Schering-Plough
	Myocet®	- Doxorubicin citrate encapsulated in liposomes - Lower clearance and higher half life of drug	Breast cancer	Elan/Sopherion therapeutics
	Marqibo®	- Vincristine sulfate encapsulated in liposomes - Lower clearance	Acute lymphoblastic leukemia	Talon Therapeutics, Inc.
	Dau-noXome®	- Doxorubicin encapsulated in non-PEGylated liposomes - Prolonged circulation time and higher accumulation in tumour site	HIV-associated Kaposi's sarcoma	Galen Pharmaceuticals
	Marqibo®	- Vincristine encapsulated in non-PEGylated liposomes - Reduced toxicity and higher accumulation in tumour site	Philadelphia chromosome-negative acute lymphoblastic leukemia	Spectrum Pharmaceuticals
	Onivyde®	- Irinotecan encapsulated in non-PEGylated liposomes - Prolonged circulation time, and higher accumulation in tumour site	Pancreatic cancer	Merrimack Pharmaceuticals
Polymer-based nanoparticle	Genexol®	- Paclitaxel in PEG-PLA copolymer micelles - Increased solubility of paclitaxel	Metastatic breast cancer and pancreatic cancer	Samyang Biopharmaceuticals
	Opaxio®	- Soluble ester conjugate of paclitaxel and $\alpha$ -poly(L)-glutamic acid - Prolonged tumour exposure of paclitaxel - Reduced neutropenia and alopecia	Ovarian cancer	Cell therapeutics
	Eligard®	- Lueprolide acetate and polymer - Prolonged drug circulation time and controlled drug release	Prostate cancer	Tolmar Pharmaceuticals

Protein-drug conjugates	Abraxane®	- Paclitaxel conjugated with albumin - Enhanced endothelial transcytosis via albumin-receptor mediated pathway	Breast cancer and non-small cell lung cancer	Abraxis Bioscience, Astra Zenica
	Ontak®	- Denileukin diftitox - Specifically targeted to T-cell	Cutaneous T-cell lymphoma	Eisai
Metal nanoparticle	Nano-Therm®	- Aminosilane-coated with superparamagnetic iron oxide - Thermal ablation by generating heat directly within the tumour tissue	Glioblastoma and prostate cancer	MagForce AG

**Abbreviation:** PEG-PLA, poly(ethylene glycol)-poly(D,L-lactide).

## Author Contributions

Y-SO, LT-HT participated in the writing of the manuscript. Y-SO conceptualized the project.

## Conflict of interest

The authors hereby declare no competing interest.

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