



Review Article

Vol. 6 (4), pp. 39 - 50, November, 2021

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Plant-derived edible nanoparticles for cancer-drug delivery: Treating the natural way

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ABSTRACT

Background: The advent of nanomaterials has brought about a paradigm shift in the diagnosis, treatment, and prevention of various chronic diseases and cancer is no exception. While these nanoparticles are highly effective, they come with their own set of perils and caveats. These concerns form the basis for numerous scientific investigations for the development of nanomedicines. This article aims to review various Plant-derived edible Nanoparticles (PDNPs) for the management of symptoms associated with various tumors and cancers.

Methods: To provide context and evidence, the relevant publications were identified on Google Scholar, PubMed, and Science-Direct using keywords such as plant-derived nanovesicles, plant-derived nanoparticles, cancer, tumors, and nanotechnology.

Results: On several grounds, the Plant-derived edible Nanoparticles (PDNPs) have demonstrated great potential against various tumors and cancers, owing to their exceptional properties. These properties include their safety profile, high stability, low immunogenicity, easy and rapid internalization by mammalian cells, and mass-production capacity. These PDNPs were also studied to present potent anti-inflammatory, anti-proliferative, regenerative, and immune modulatory properties, and are stable in the gastrointestinal tract upon oral administration.

Conclusions: This article aims to critically review various PDNPs that have been studied over the years and to demonstrate their promising role in managing and alleviating the symptoms associated with cancers. However, more conclusive evidence is recommended from various preclinical and clinical studies to corroborate their safety, efficacy, and toxicity profiles in various patient cohorts, before establishing it as a novel drug delivery modality.

Keywords: Plant products, Edible nanoparticles, Cancer-drug delivery, Natural products.

INTRODUCTION

In the quest for the development of newer and more potent treatment modalities against various diseases, researchers must address a multitude of challenges including drug delivery concerns, safety and toxicity profiles, production costs, target specificity, and potential adverse effects. Several studies have underscored the utility of artificially manufactured Nanoparticles (NPs) in the delivery of modest concentrations of medicaments (such as peptides, proteins, and siRNAs) to specific types of cells and receptors (Laroui et al., 2010, 2012; Laroui, Geem, et al., 2014; Laroui, Theiss, et al., 2011; Laroui, Viennois, et al., 2014; Laroui,

Wilson, et al., 2011; Wilson et al., 2010; Xiao, Laroui, et al., 2014; Xiao, Si, et al., 2015; Xiao, Yang, et al., 2014; Xiao, Zhang, et al., 2015; Xiao et al., 2013; Xiao and Han, et al., 2015; Xiao and Merlin, 2012). Despite having an arsenal of nanotechnology-based drug delivery modalities, two key limitations are still under-addressed. Firstly, each element of the formulated nanoparticle must be tested for possible *in vivo* toxicity before clinical administration. Secondly, their utility is limited, owing to the challenges faced during mass production. However, these limitations could be addressed by employing nanoparticles derived from natural sources such as plants and herbs (Mingzhen Zhang et al.,

2016). The current treatment regimen for most difficult-to-manage and chronic diseases, such as cancer, cardiovascular disease, diabetes, and neurological disorders, includes protein therapeutics (Leader et al., 2008; Morrison, 2016). However, this is currently limited to extracellular targets, due to the inability of protein drugs to enter mammalian cells. The exosomes are natural nanovesicles that circulate within the mammalian body, possessing an intrinsic ability to deliver drug moieties (especially, peptides and protein therapeutics) into intracellular targets. Over the recent years, the exosomes have gained considerable attention, but their efficiency as a potential vehicle for drug delivery needs to be thoroughly corroborated using both preclinical and clinical studies (Hung and Leonard, 2016; Mangeot et al., 2011; Marcus and Leonard, 2013; Stickney et al., 2016). These exosomes are extracellular vesicles enclosed within a lipid-bilayer and have been studied to transfer proteins, nucleic acids, and lipids between the cells (Cocucci et al., 2009; Colombo et al., 2014; Kowal et al., 2014). Exosomes circulate in the blood (Akers et al., 2013; Gutierrez-Vazquez et al., 2013; Mittelbrunn and Sanchez-Madrid, 2012), and are conspicuously found in most bodily secretions such as, breast milk (Izumi et al., 2015; Wolf et al., 2015), saliva (Byun et al., 2015; Wong, 2015; Zlotogorski-Hurvitz et al., 2015), serum (Akers et al., 2013; Almqvist et al., 2008; Gutierrez-Vazquez et al., 2013; Mittelbrunn and Sanchez-Madrid, 2012; Rupp et al., 2011; Tanaka et al., 2013), urine (Nilsson et al., 2009; Z. Wang et al., 2012; Zhou et al., 2006) and extravasations from malignant tissues (Bard et al., 2004; Cappellesso et al., 2014). Additionally, a plentitude of mammalian cells, such as cancer cells (Lehmann et al., 2008), dendritic cells (Morelli et al., 2004), epithelial cells (Van Niel et al., 2001), immune cells (Skokos et al., 2003; Stenqvist et al., 2013), and platelets (Robertson et al., 2006), have been studied to effuse exosomes (Mingzhen Zhang et al., 2016). The success of their utility as a drug delivery modality is attributed to the specific surface-membrane protein interactions, that facilitate identification and endocytosis by tissue cells, further helping them efficiently deliver drugs (Heusermann et al., 2016; Svensson et al., 2013; Tian et al., 2014]. Recent studies have also shown their profound role in cell signaling, cell communication, inflammation, tumor metastasis, tissue repair, immunity, immunodefense, and pathogendissemination (Beyer and Pisetsky, 2010; Costa-Silva et al., 2015; Gutierrez-Vazquez et al., 2013; Mahmoodzadeh Hosseini et al., 2013; Melo et al., 2015; Meyer et al., 2017; Peinado et al., 2012; Raposo et al., 1996; Sung et al., 2015; They et al., 2009). The endogenous nature of exosomes for the transport of a multitude of biomolecules has led to the development of exosome-based vehicles for the delivery of therapeutic drugs (Simpson et al., 2008; Valadi et al., 2007; Vlassov et al., 2012). By virtue of the bioactive delivered, the exosomes can also exert

their influence on gene and protein expressions, and have been identified by exosomal protein biomarkers such as CD9, CD63, CD81, and Hsp70 (Caby et al., 2005; Mingzhen Zhang et al., 2016). However, their current utility is impeded by our understanding of the synthesizing, characterizing, and engineering of exosomes to deliver a spectrum of chemical moieties, as well as to increase their uptake by target cells (Meyer et al., 2017).

PLANT-DERIVED EDIBLE NANO-PARTICLES (PDNPs)

In recent years, growing bodies of evidence have suggested the release of extracellular exosomes from plant cells. They have also underscored its imperative role in cellular signalling and communication between plant cells (Raimondo et al., 2015). Several studies have also highlighted its similarity with mammalian cells, on grounds such as structure, content, and mechanism of release (Perez-Bermudez et al., 2017). Owing to the fact that their quantity increases in the presence of external or internal stress factors, their secretion is linked to multi vesicular body secretions outside the cell (An et al., 2007). However, researchers have differentiated the PDNPs from their mammalian counterparts on the variations in the lipid and miRNA compositions. The PDNPs were studied to have higher phospholipid levels (~98%), while their mammalian counter parts demonstrated higher levels of cholesterol (Mingzhen Zhang, Viennois, Xu, et al., 2016). Furthermore, these PDNPs have also exhibited potent anti-proliferative and anti-cancer properties, despite substantial evidence of their underlying processes (Benavente-Garcia and Castillo, 2008; Blagosklonny, 2005; Manthey et al., 2001; Liwen Wang et al., 2014). While most synthetic nanoparticles (e.g. liposomes) suffer from several limitations, such as toxicity, poor oral bioavailability, and insufficient tissue distribution, PDNPs are known to overcome these obstacles (K. Cho et al., 2008; Sarvarian et al., 2021; Mingzhen Zhang et al., 2017). Therefore, these factors provide a great advantage for PDNPs, breaking new grounds for potential utility. Additionally, because of their natural origin from edible plants such as broccoli, ginger, grapefruit, grapes, and lemon, the PDNPs are non-toxic and pose low immunogenicity. Furthermore, they are highly tissue-specific, demonstrate a high level of internalization, and could be synthesized in enormous amounts. Furthermore, their lipophilicity facilitates them to penetrate the Blood-Brain Barrier (BBB), but not the placenta. Thus, these PDNPs are well suited for use as a therapeutic drug carrier (Sarvarian et al., 2021; C. Yang et al., 2018). Compared to other artificially synthesized carriers, PDNPs also regenerate and rejuvenate intestinal tissue on oral administration. In healthy patients, depending on their constituent lipid and miRNA content, they alter the gut micro biota and the immune cells, thereby exhibiting a crucial role

in battling inflammatory diseases, like liver steatosis, injuries associated with colitis, and even malignancies in colorectal cancer (Rome, 2019; Sarvarian et al., 2021). From a drug delivery perspective, loading of therapeutic moieties such as proteins, peptides, siRNAs, and DNA expression vectors could be easily achieved, following which the drug could be transported to particular tissues in various anomalies (Sarvarian et al., 2021). Thus, this could open new horizons for the delivery of small-molecule drugs and large biological moieties for the treatment of various malignancies and cancers, which are currently impeded by the current drug delivery modalities.

PHYSICOCHEMICAL PROPERTIES AND CHARACTERISTICS OF PDNPS

Structure

The general configuration of most PDNPs is a spherical and primitive lipid bilayer that closely resembles the eukaryotic cell membrane (B. Wang et al., 2014; C. Yang et al., 2018). They also share characteristic similarities with the mammalian cell-derived exosomes, extracellular vesicles, and other synthetically formulated drug vectors, like liposomes (L.-M. Mu et al., 2017; Vader et al., 2016; C. Yang et al., 2018).

After lipid extraction and consecutive reassembly, PDNPs can be synthesized into a wide variety of multilayered structures (C. Yang et al., 2018). Wang et al., opine that the grapefruit-derived NPs reassembled to yield a unique multilayered flower-like structure, which could be leveraged for the transport of siRNAs, peptides, proteins, and a spectrum of small-molecule chemotherapeutic molecules (Q. Wang et al., 2013). Another team of researchers coated these grapefruit-derived NPs with a blood cell-derived plasma membrane to formulate a multilayered substructure. PDNPs encapsulated within the plasma membrane-derived vesicle, successfully delivered to the inflamed tumor site (Q. Wang et al., 2015).

Physical properties

Generally, the size of the naturally occurring PDNPs falls in a spectrum of 30 to 500 nm. However, structures <30 nm have been studied to be unstable and to demonstrate low drug loading capacity, owing to the difficulty of packing the lipids on a highly curved surface (Milcovich et al., 2017; C. Yang et al., 2018). While the ginger-derived nanoparticles form spherical lipid bilayers of a size approximating 220-290 nm (Mingzhen Zhang et al., 2016), the grapefruits assemble into a multi layered flower-like structure of about 180-200 nm size (Q. Wang et al., 2013). However, by modulating the dispersity of nanoparticle extrusion, the diameter of PDNPs can be altered (Mingzhen Zhang et al., 2016). Furthermore, the sizes of PDNPs are greatly

influenced by pH, and thus their diameters could be modulated by altering pH (J. Mu et al., 2014). However, a change in pH may have profound effects on the size, diameter, and population characteristics. These changes could direct the PDNPs to shrink, swell, coalesce, separate into sub-populations of variable sizes, or to amalgamate into a single population of uniform size (C. Yang et al., 2018). In addition, similar to eukaryotic cells, the PDNPs also bear a negative potential on their surface, which has been corroborated by the zeta potential results (Deng et al., 2017; Siontorou et al., 2017; Q. Wang et al., 2015; C. Yang et al., 2018). Furthermore, exposure of carrot, grapefruit, and grape-derived NPs to a stomach-like pH significantly reduced the negative charge of these PDNPs, primarily due to neutralization by the acidic solution. However, there was no change observed on introducing the latter to an intestine-like pH (J. Mu et al., 2014; C. Yang et al., 2018).

Chemical properties

The chemical composition of PDNPs differs considerably from those of their mammalian cell-derived counterparts. The exosomes released from mammalian cells demonstrate a high proportion of cholesterol, glycosphingo lipids, and phosphatidyl serine in their bilayer, all accounting for their characteristic membrane rigidity (Ha et al., 2016; Stremersch et al., 2016; C. Yang et al., 2018; Mingzhen Zhang et al., 2016). Additionally, a similar chemical composition also forms the basis for the development and stability of most synthetically formulated nanoparticles, such as liposomes (Siontorou et al., 2017; C. Yang et al., 2018; Zylberberg and Matosevic, 2016). However, PDNPs have been investigated to be devoid of any cholesterol. Additionally, the mammalian cell-derived NPs contain significantly more protein content, compared to the PDNPs (Mathivanan et al., 2012; Mingzhen Zhang et al., 2016; Mingzhen Zhang et al., 2016). Nevertheless, the total concentration of mRNAs, miRNAs, and non-coding RNAs, are similar in the PDNPs and the mammalian cell-derived exosomes (Kowal et al., 2016; Mingzhen Zhang et al., 2016). The lipid composition of the ginger-derived nanoparticles showed substantial levels of Phosphatidic Acids (PA) (25-40%), Digalactosyl Diacyl Glycerol (DGDG) (25-40%), and Mono Galactosyl Diacyl Glycerol (MGDG) (20-30%) (Mingzhen Zhang et al., 2016). However, a similar assay on the Grape exosome-like nanoparticles demonstrated high levels of PA (53.2%), and Phosphatidyl Choline (PC) (9.03%), and Phosphatidyl Ethanolamine (PE) (26.1%), in their membranes (Ju et al., 2013). Furthermore, studies on grapefruit-derived nanovesicles have demonstrated higher levels of PC and PE, further accounting for their anti-colitic, anti-inflammatory, and antioxidant properties (J. Y. Cho et al., 2011; Sarvarian et al., 2021; Stremmel et al., 2005). Moreover, the major flavanone in grapefruits, naringin, has been

studied to be converted to naringenin by the gut microbiota. This further broadens its utility, due to its anti-cancer, anti-colitis, anti-inflammatory, and anti-oxidative properties (Amaro et al., 2009; Dou et al., 2013; Sarvarian et al., 2021). In addition, recent studies have elucidated the relatively high protein concentration in Citrus limon-derived NPs. Comparison of the protein dataset of these NPs to those of mammalian cell-derived ones, revealed a 57% similarity index, suggesting an overlap of constituent proteins (Raimondo et al., 2015; Sarvarian et al., 2021). Conclusively, the results of these studies suggest and direct towards the biocompatible and low-immuno genetic utility of various PDNPs in various drug delivery and carrier systems.

Isolation, purification, and characterization of PDNPs

The most common method for the isolation of PDNPs is differential ultracentrifugation with a density gradient. Firstly, plant juices are centrifuged at low speeds to remove plant debris and fibres. Subsequently, the resultant solution is subjected to medium-speed centrifugation to extract the remaining particles and organelles, following which high-speed centrifugation yield exosome-like nanovesicles and other PDNPs. Additionally, other biological components, including proteins and RNAs, are also precipitated using this method. The PDNPs are thus segregated from the other cellular components by varying the densities and employing the sucrose-density gradient (Di Gioia et al., 2020; Sarvarian et al., 2021; Mingzhen Zhang et al., 2016). Although the methodology seems fairly simple, the type, quantity, and quality of isolated PDNPs are greatly influenced by the type of rotor (fixed angle or swinging bucket), g-force, angle of rotor sedimentation, the radius of centrifugal force,

solution viscosity, and pelleting efficiency (rotor and tube K-factor) (Lakhal and Wood, 2011; Sarvarian et al., 2021; Taylor and Gercel-Taylor, 2008; Zhou et al., 2006). While methods such as immune isolation and ultrafiltration employed to obtain purer preparations of animal-derived exosomes can be extrapolated for the isolation of PDNPs, these methods pose some drawbacks, including the incurrence of higher costs, which impedes their utility for PDNPs (Akuma et al., 2019; Di Gioia et al., 2020; Raimondo et al., 2019).

Similar to the methods used to elucidate subcellular ultra-structures, Transmission Electron Microscopy (TEM) is used to characterize and describe PDNPs, although this approach does not provide mechanical or biochemical information (Chevillet et al., 2014; Gangalum et al., 2011; Sarvarian et al., 2021; Van Der Pol et al., 2010). Dynamic Light Scattering (DLS) or Photon Correlation Spectroscopy (PCS) is a simple, accurate, and widely used method for determining the size-dispersion status of the nanoparticles in a PDNP-suspension. It also estimates the zeta potential of PDNPs (J. Mu et al., 2014; Sarvarian et al., 2021; J. Yang et al., 2014; M.-Z. Zhang et al., 2014). Recently, advanced methods such as Atomic Force Microscopy (AFM) have been used to profile the size and structure of various PDNPs (Sarvarian et al., 2021; Sharma et al., 2010). Another technique employed for the quantification of PDNP size is Nanoparticle Tracking Analysis (NTA). This process determines the size of the NPs between 30 nm and 1 μ m, by real-time tracking of Brownian motion, accounting for the high accuracy of PDNPs in biological fluids (Carnell-Morris et al., 2017; McNicholas and Michael, 2017; Sarvarian et al., 2021). Figure 1 illustrates the process of isolation, purification, and characterization of PDNPs.

Isolation, Purification and Characterization of PDNPs for drug delivery

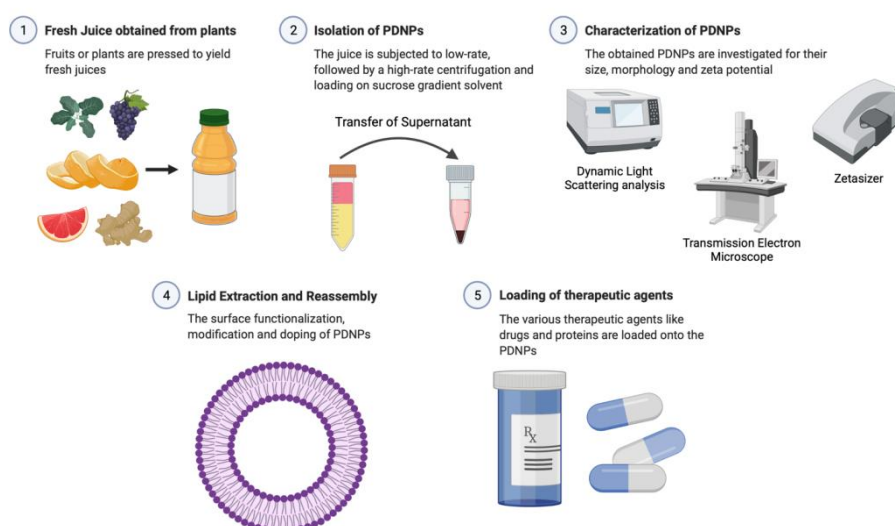


Figure 1. Isolation, purification and characterization of PDNPs for anticancer drug delivery.

CURRENT CANCER TREATMENT REGIMEN AND ITS LIMITATIONS

Cancer is one of the leading causes of death worldwide, with an estimated 7.6 million deaths per year and contributing 13% of all deaths (Barnard, 2004; Gmeiner and Ghosh, 2014; Jemal et al., 2018; Sarvarian et al., 2021; Libin Wang et al., 2018). The current line of treatment emphasizes the use of conventional strategies such as chemotherapy, radiation therapy, and several other surgical interventions (Gmeiner and Ghosh, 2014; Ocana et al., 2011; Sarvarian et al., 2021). Despite these efforts, the rate of cancer recurrence, as well as the failure of treatment, has increased substantially over the last few decades (Gmeiner and Ghosh, 2014; Wculek and Malanchi, 2015). From a drug delivery perspective, the chemotherapeutic agents are mostly non-selective, and thus, cannot differentiate between malignant and healthy tissues. Additionally, limited permeability and penetration into the cells, non-selective uptake by healthy cells, and rapid *in vivo* metabolism compromise the treatment regimen while exerting toxic effects on the healthy tissues (Irvani and Varma, 2019; Sarvarian et al., 2021; Q. Wang et al., 2013). However, the employment of NP-based interventions addresses these issues arising due to the latter. Although lipid-based NPs such as liposomes are the most preferred drug delivery system, most synthetically formulated NPs show adverse effects following inflammation, cell stress, and eliciting an immune response, and eventually the apoptotic cascade (Allen and Cullis, 2013; Sarvarian et al., 2021; Xiao et al., 2015; Ming-Zhen Zhang et al., 2013). Thus, employing the PDNPs cater to all these issues, thus presenting a potential treatment intervention and drug delivery modality in chronic conditions, especially malignancies and localized cancers.

PDNPS IN CANCER DRUG DELIVERY

At the outset, the current chemotherapeutic regimen poses a spectrum of shortcomings, such as toxicity, lack of target specificity, which beget adverse reactions, thereby defeating the treatment objective. While nanoscale drug carriers, such as polymeric NPs, organic and inorganic biomaterials, are believed to be the panacea for all these problems, they pose their own set of limitations (Lu et al., 2017). Unlike liposomes, perhaps the most significant utility of PDNPs is the delivery of anticancer therapeutics, without inducing damage to the cell and cellular components (Di Gioia et al., 2020).

Grapefruit-Derived Nanoparticles (GFDNPs)

A recent study incorporated inflammatory-related receptor enriched membranes of activated leucocytes on Grapefruit-Derived lipid NPs (GFDNPs). These GFDNPs were successfully formulated to deliver doxorubicin to the inflamed cancerous tissue. They also used murine models to

conclude that these receptor-enriched membranes demonstrated better tumour targeting than GFDNPs (Q. Wang et al., 2015). GFDNPs were also employed for co-delivering the therapeutic moieties and folic acid, which further enhanced the targeting efficiency towards cells expressing folate receptors. Additionally, these GFDNPs substantially improved the chemotherapy-induced tumour growth inhibition in CT26 and SW620 cell-derived tumours in murine models. Furthermore, intravenous administration of these GFDNPs in pregnant mice did not cross the placental barrier, further indicating their potential as a drug delivery system (Q. Wang et al., 2013). GFDNPs functionalized with Folic Acid (FA) were also utilized for intravenous administration of Paclitaxel (PTX) to tumour tissue. The enhanced targeting efficiency and substantial reduction in tumour sizes in mice xeno grafted with CT26 or SW620 cells are attributed to overexpression of FA receptors on tumour cells (Gali-Muhtasib and Chouaib, 2020). However, intranasal administration of GFDNPs could transport the anti-signal transducer and activator of the transcription 3 (Stat3) inhibitor JSI-124 to the brain, thus inhibiting implanted GL26 tumour growth. The objective of this treatment regimen is to reduce the pro-inflammatory and pro-tumoral effects of the microglial and resident macrophages of the brain (Zhuang et al., 2011). Additionally, the intranasal delivery of JSI-124-loaded GFDNPs (12.5 pmol) for 10 days, without free JSI-124 or plain GFDNPs, substantially reduced the size of the tumour 15 and 20 days after the injection, subsequently prolonging the survival of the mouse (Q. Wang et al., 2013). Another study concluded the selective uptake of GFDNPs by intestinal macrophages, which facilitated the alleviation of dextran sulphate sodium-induced colitis in mice (B. Wang et al., 2014). Moreover, their biocompatibility, non-toxic nature, biodegradability, and stability across a spectrum of pH values, corroborate their utility as an oral drug delivery system. The loading of Methotrexate (MTX) into these GFDNPs exhibited lowered toxicity and significantly better therapeutic outcomes, against free MTX in dextran sulphate sodium-induced murine colitis. In addition, GFDNPs have been proposed to promote macrophage homeostasis and modulate the immunological response in the colon. Therefore, the utility of GFDNPs could be extrapolated for the oral delivery of drugs targeting inflammatory diseases in humans (Gali-Muhtasib and Chouaib, 2020; B. Wang et al., 2014). Thus, with further preclinical and clinical studies, these GFDNPs could be a potential drug delivery modality for delivering anticancer drugs to tumorous tissue.

Ginger-Derived Nanoparticles (GDNPs)

To achieve better targeting of the NPs toward cancer tissues, researchers functionalized these nanovectors with Folic Acid (FA), which exhibited a greater affinity in binding to the folate receptors, overexpressed in tumour cells but nearly absent in

the healthy cell surface. These FA-nanovectors were tested as a vector for the delivery of doxorubicin in the management of colon cancer. In a trial involving the treatment of colon cancer, Zhang et al. reported the improved drug delivery of GDNPs upon conjugation with the targeting ligand FA. The doxorubicin was fully loaded into FA-GDNPs, which were then efficiently taken up by colon cancer cells, demonstrating excellent biocompatibility and efficiently inhibiting tumour development. Furthermore, compared to most commercially available drug delivery vehicles, these FA-GDNPs released doxorubicin much rapidly in the acidic pH, which mimics the tumour environment. These properties of FA-GDNPs were attributed to reduced systemic toxicity of the drug, with a concurrent increase in the circulation time (~48 hours), thereby improving its efficacy against the tumors (Mingzhen Zhang, Xiao, et al., 2016). Using Colitis-Associated Cancer (CAC) murine models, the authors also demonstrated that the administration of GDNPs (0.3 mg protein/mouse by gavage, every day for 49 days) could limit the tumour growth by mitigating the intestinal epithelial cell (IEC) proliferation (Mingzhen Zhang et al., 2016). GDNPs also suppress IEC by suppressing pro-inflammatory cytokines or chemokine's, such as IL-1, IL-6, and TNF- α . Concurrently, the administration of GDNPs promotes the expression of proteins such as cGMP-dependent kinase and transgelin, which are generally down-regulated in human colonic cancers (Di Gioia et al., 2020). Thus, these results could blaze new trails and provide a lead for future research for nature-derived cancer drug delivery vectors.

Lemon-Derived Nanoparticles (LDNPs)

The utility of PDNPs in cancer treatment and inhibition of cell proliferation in various cancer cell lines has been well established (Gali-Muhtasib and Chouaib, 2020; Sagini et al., 2017). Research conducted by Raimondo et al. substantiated the presence of nanoparticles in Citrus limon. These Lemon-derived NPs (LDNPs) were isolated using

the ultracentrifugation technique, followed by purification in a 30% sucrose gradient. Additionally, these LDNPs were used to treat cells in a dose and time-dependent fashion, where the growth of all three cell lines namely, A549, LAMA84, SW480 were impeded. Furthermore, treating the healthy cell lines with the LDNPs did not hinder their development, corroborating their specificity towards cancer cells. Furthermore, the study also reported an increased expression of pro-apoptotic molecules (Bax) along with a concurrent decrease in the expression of anti-apoptotic molecules (Bcl-xl and survivin) expression in the LAMA84 cell line. Additionally, compared to the control group, pro-angiogenic factors such as IL-6, IL-8, and Vascular Endothelial Growth Factor-A (VEGF-A) were significantly lower in the LAMA84 cell line and serum of mice treated with LDNP. Concurrently, these nanovesicle-treated cancer cell lines confirmed increased production and release of TNF-related apoptosis-inducing ligands (TRAIL), which were significantly higher in the LAMA84 cell line, compared to others. In addition, the potential of LDNPs to reduce tumour growth was investigated in an *in vivo* tumor xenograft. These findings underscore the potential of LDNPs in the suppression of cytokine secretion, while concurrently mitigating tumour growth *via* the TRAIL-mediated apoptosis pathway. The optical imaging of the intraperitoneally administered lipophilic fluorescent tracer DiR-labelled LDNPs underscored their quick delivery to tumorous tissues in murine models (Raimondo et al., 2015). However, the mechanism by which LDNPs reduce chronic myeloid leukaemia xenograft tumour growth in animal models is still unknown (Raimondo et al., 2015; Sarvarian et al., 2021). Thus, more research and preclinical studies are suggested on this subject to obtain more articulate data and a deeper understanding of its mechanism in tumour suppression. Table 1 summarizes the various PDNPs that have been studied for the effective delivery of anticancer drugs in various cancer cell lines.

Table 1. Various PDNPs studied for effective delivery of anticancer drugs.

Sr.No.	Source	Pharmaceutical Agent	Target	References
1.	Apple	miRNAs	Human epithelialcolorectal adenocarcinoma cells (CaCO ₂)	(Fujita et al., 2018)
2.	Broccoli	Sulforaphane	Colon tissue	(Deng et al., 2017)
3.	Ginger	Doxorubicin	Colon cancer cell lines	(Mingzhen Zhang et al., 2016)
		siRNA-CD98	Colon-26 cells, RAW 264.7 macrophages	(Mingzhen Zhang et al., 2017)
		miRNA, 6-gingerol, 6-shogaol	Intestinal Epithelial Cells (IEC)	(Mingzhen Zhang, et al., 2016)
4.	Grapefruit	Doxorubicin, curcumin	Colon cancer	(Q. Wang et al., 2015)
		JSI-124 (anti-Stat3 inhibitor), Paclitaxel (PTX), luciferase gene siRNA	Tumour cells 4T1, GL26, A549, CT26, SW620	(Q. Wang et al., 2013)
		miR17	GL26 brain tumor cells	(Zhuang et al., 2016)

		Methotrexate	Intestinal macrophages	(B. Wang et al., 2014)
		miR-18a	Liver Kupffer cells	(Teng et al., 2016)
5.	Lemon	Proteins	Chronic Myeloid Leukemia (CML)	(Raimondo et al., 2015)

DISCUSSION AND CONCLUSION

At the outset, in the nanomedicinal field, the PDNPs have exhibited various useful properties such as high internalization rate, relatively low immunogenicity, stability in the GIT, and the propensity to overcome the blood-brain barrier while not crossing the placental barrier. They have also shown anti-inflammatory and regenerative properties, which could facilitate their use in chronic inflammatory disorders, such as those that affect the lungs or the central nervous system. Usually, non-targeted chemotherapy is applied in the treatment of cancers. However, this method is unable to differentiate between normal healthy cells and cancerous cells, which can lead to severe toxic side effects and insufficient therapeutic action. Here, the application of PDNPs would not only allow for targeted chemotherapeutic drug delivery but also lower the toxic side effects, as they are inherently non-toxic and also free from immune toxicity. These nanovesicles from edible plants are one of the safest and most cost-efficient targeted drug delivery platforms, as they are more biocompatible, and can be produced relatively cheaper on a large scale. However, the mechanism of action of these PDNPs is still unclear, which could lead to unforeseen side effects due to their pleiotropic nature. Moreover, no evidence is available which demarcates the differences in nanovesicles obtained from different parts of the source plant, e.g., those obtained from the roots compared to those obtained from the leaves. Hence, detailed studies on the safety aspects of PDNPs in animal models, as well as reports on their pharmacokinetics and pharmacodynamics, are necessary before they can be brought into a clinical setting. Lastly, further research and more clinical trials, especially in diseases like brain cancer are required to bring to light their therapeutic mechanisms.

ACKNOWLEDGEMENTS

The images have been created using BioRender.com

AUTHOR CONTRIBUTIONS

Conceptualization: AN; RV
 Validation: AN; RV
 Resources: AN; RV; SS
 Data curation: RV; SS
 Writing-Original Draft: RV; SS
 Writing-Review and Editing: AN; RV
 Visualization: RV
 Supervision: AN.
 Project administration: AN; RV

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

FUNDING

No funding was received for this work.

ETHICAL STATEMENT

No ethical approval was required as this study did not involve human participants or laboratory animals.

DATA AVAILABILITY

Data sharing is not applicable as no new data was created or analyzed in this study.

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