ISSN 2745-455X (Online)
Indonesian Journal of Pharmacology and Therapy

Clinical application of dendrimer in cancer and COVID-19 therapy: a review

Ninda Devita[1,2]*, Nurfadilah[1], Siti Khadijah[1], Ulil Albab Habibah[3]

[1]Magister Program of Biomedical Sciences., Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, [2]Department of Microbiology, Faculty of Medicine, Universitas Islam Indonesia, Yogyakarta, Indonesia, [3]Faculty of Medicine, Universitas Islam Indonesia, Yogyakarta, Indonesia

https://doi.org/10.22146/ijpther.2311

Submitted: 05-08-2021
Accepted : 04-03-2024

Keywords:
dendrimer;
cancer;
COVID-19;
diagnosis;
therapy

ABSTRACT

Dendrimers are nanoparticles with unique characteristics. These characteristics allow these nanoparticles to be widely applied in medicine. It can be used as a therapy for various types of cancer. The dendrimers can also been use an alternative to accelerating the diagnosis and therapy of COVID-19. This review aimed to delve deeper into the myriad clinical applications of dendrimers in the treatment of various cancers and its potential use for the treatment or diagnosis of COVID-19. The databases used for this review were Google Scholar and Science Direct. The inclusion criteria for this review are articles published in 2018-2023. Articles other than the original articles and reviews we excluded from the study. Anticancer formulated in dendrimers have a better ability to eradicate cancer cells in the treatment of breast, colon, lung, prostate, skin, ovarian, and liver cancers compared to ordinary anticancer agents. Dendrimer *in vivo, in vitro* and phase II clinical trials can be used to deliver miRNA therapy or symptomatic drugs in COVID-19 patients and as vaccine delivery agents. The quality of molecular diagnosis of COVID-19 can also be improved with these nanoparticles. The use of dendrimers can improve the quality of management of cancer and COVID-19 patients.

ABSTRAK

Dendrimer adalah nanopartikel dengan karakteristik unik. Karakteristik ini memungkinkan nanopartikel ini diterapkan secara luas dalam dunia kedokteran. Dendrimer dapat digunakan sebagai terapi berbagai jenis kanker. Dendrimer juga dapat menjadi salah satu alternatif dalam mempercepat diagnosis dan terapi COVID-19. Tujuan dari tinjauan ini adalah untuk mempelajari lebih dalam tentang berbagai aplikasi klinis dendrimer dalam pengobatan berbagai jenis kanker dan potensi penggunaan dendrimer untuk pengobatan atau diagnosis COVID-19. Database yang digunakan untuk review ini adalah Google Scholar dan Science Direct. Kriteria inklusi review ini adalah artikel yang diterbitkan pada tahun 2018-2023. Artikel selain laporan penelitian dan artikel ulasan kami eksklusikan. Antikanker yang diformulasikan dalam dendrimer memiliki kemampuan yang lebih baik dalam mengeradikasi sel kanker pada pengobatan kanker payudara, usus besar, paru-paru, prostat, kulit, ovarium, dan hati dibandingkan dengan obat antikanker biasa. Penelitian *in vivo*, *in vitro* dan fase II menunjukkan dendrimer dapat digunakan sebagai pembawa terapi miRNA, obat simtomatik, bahkan vaksin pada pasien COVID-19. Kualitas diagnosis molekuler COVID-19 juga dapat ditingkatkan dengan nanopartikel ini. Penggunaan dendrimer dapat meningkatkan kualitas penanganan pasien kanker dan COVID-19.

*corresponding author: ninda.devita@uii.ac.id

INTRODUCTION

Nanotechnology brings breakthroughs to the world of medicine. Nanotechnology has been widely used to improve diagnostic ability, therapeutic accuracy, and disease follow-up.[1] A dendrimer is one type of polymer nanoparticle that has a unique structure. Dendrimer consists of a core with branches called generations. Each generation is assigned a generation number indicating the number of branching reactions carried out to the nuclear molecule.[2,3] The more generations cause an increase in size, the shape becomes more globular and the flexibility of the dendrimer.[4] The end of the branch is a multivalent surface that can be modified. This modification involves adding functional groups such as COOH, COONa, NH2, or OH.[5] This surface functionalization can reduce the rate of clearance by the reticuloendothelial system, and increase the efficiency of transporting molecules, and the release of molecules carried.[2] FIGURE 1 shows the basic structure of dendrimer with three generations.

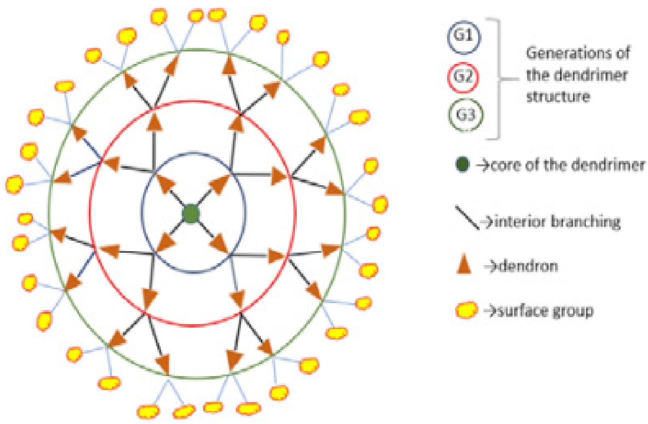

FIGURE1. Structure of dendrimer.[1]

Among the many types of nanoparticles available, dendrimers offer many advantages. Dendrimers are good drug carriers because they easily penetrate cells transcellular and paracellularly. Dendrimer nanostructures facilitate the passive entry of drugs into cells by increasing the permeability of the molecules carried. The dendrimer structure facilitates administration via oral, parenteral, pulmonary, or nasal. Both hydrophilic and lipophilic drugs can be carried by dendrimers. The more branches during the synthesis process cause the shape of the dendrimer to be stronger and narrower polydispersity. Dendrimers can be functionalized multiple times and can be conjugated with high-density molecules. The dendrimer surface is easily modified so that the pharmacokinetic and pharmacodynamic parameters are easily controlled.[3,6,7]

Dendrimer is widely used in medicine. Dendrimers are used as protein analogs or enzymes that are easy to functionalize. Dendrimer as a drug delivery agent has been used in several therapies such as the treatment of HIV infection, anti-inflammatory, anti-Alzheimer, anticoagulation, and anti-cancer. A dendrimer is also useful for improving the performance of a disease diagnosis. Dendrimers can be used as carriers for imaging sensor agents. Dendrimers can increase the penetration of sensory agents so that the specificity and sensitivity of imaging increase. Gallium-68 [68Ga] is a radioisotope for n-positron emission tomography (PET) examination. Gallium bound by the dendrimer can increase the infiltration of substances into the tumor tissue so that the resulting PET images are clearer.[3,4,8]

Cancer is one of the diseases that cause death every year, without definite therapy. The development of medical knowledge triggered the development of therapies to control cancer more optimally. The development of polymers as cancer therapy agents is developed from year to year but is constrained by chemical structures such as polymer weight and polydispersity. The development of dendrimer-based aptamer therapy is expected to provide advantages as the latest cancer therapy agent. A study in 2021 showed that dendrimers containing gefitinib and photosensitizer hematoporphyrin (Hp) can prevent hypoxia and overcome therapy resistance in non-small cell lung carcinoma patients in combination with photodynamic therapy. Dendrimer-based therapy can improve solubility, bioavailability, and drug target accuracy. Dendrimers can deliver drugs to targets with high safety and reduce the toxicity of the drug itself.[9,10]

The use of dendrimers as antiviral drug carriers has been tried in several viruses such as influenza, Ebola, Zika, HSV-1, HSV-2, and HIV.[11] Study on HIV shows that decoy RNA formulated into dendrimers can inhibit the life cycle of HIV, effectively deliver into lymphocytes, and cytoprotective against HIV infection. The study is also developing an Ebola vaccine with a dendrimer as an alternative carrier.[12]

COVID-19 is caused by the SARS-CoV-2 virus. This virus quickly spread to cause a pandemic. The condition of a COVID-19 patient can quickly deteriorate. Dendrimers can increase the bioavailability and stability of drugs. Dendrimer-based therapy may help the patient recover.[13] A study on mERS-

CoV-2, a virus that is related to SARS-CoV-2, showed that the use of dendrimers could increase the antiviral delivery and antiviral effects of the drug.[14]

Dendrimers have been used in many anticancer therapy studies. COVID-19 is an emerging disease that requires breakthroughs in handling it. In this review, we aim to delve deeper into the myriad clinical applications of dendrimers in the treatment of various cancers and the potential use of dendrimers for the treatment or diagnosis of COVID-19.

MATERIAL AND METHODS

International and national journals as references were selected in writing this review through Google Scholar and Science Direct databases. The keywords used in the search in both databases included "dendrimer AND cancer therapy", "dendrimer AND COVID-19" "diagnosis", and "dendrimer AND COVID-19 therapy". Boolean logic "AND" is used to get specific results. We then arrange the search result data by topic. Search results that met the inclusion and exclusion criteria were arranged systematically. The inclusion criteria for this review are articles published in 2018-2023. Articles other than the original articles and reviews we excluded from this study.

RESULT AND DISCUSSION

There were 32 selected sources in the references, which comprised 15 review articles and 17 studies. The articles about cancer 19 articles (6 reviews and 13 research articles) and 13 articles (9 reviews and 4 research articles about COVID-19).

Dendrimer for cancer therapy

Chemotherapy, radiotherapy, and surgery are the first choices for cancer treatment but have not provided maximum safety and effectiveness. The new treatment is also limited because it is harmful to healthy cells and risks lowering the patient's immune quality. In other sources, chemotherapy is at risk for growing other types of cancer. Therapies that have minimal side effects and effectively kill cancer cells need to be developed to help patients. The development of nanotechnology-based dendrimers is expected to be able to effectively kill tumor cells without the need to harm healthy cells.[15,16]

The advantage of dendrimer-based cancer therapy over other therapies is that dendrimers can target and enter tissues selectively at the molecular level, able to increase cellular uptake and localization of the drug, and accurate and targeted drug delivery accuracy to cancer cells without interaction with healthy cells. In contrast to the dose levels required from previous cancer treatments. The use of dendrimer drug agents allows lower doses due to drug or small molecule encapsulation due to drug or small molecule encapsulation. Although the dose used is lower, dendrimers allow higher solubility than pre-existing treatments. Encapsulation using dendrimers also increases the level of precision in delivery in delivering drugs to small areas in the body. The very interesting thing about this dendrimer is that it can reduce the risk of resistance that generally arises in the use of chemotherapy-type therapy.[15,17]

The other advantages possessed by dendrimers are inseparable from side effects such as excessive production of reactive oxygen species (ROS) which will increase oxidative stress and DNA damage. The long-term impact of oxidative stress is Alzheimer's disease and Parkinson's disease. The selective target of the dendrimer is like a double-sided coin because in cancer patients normal cell surface proteins will usually be abnormally overexposed which will affect the selectivity of the dendrimer drug agent itself.[18]

The use of dendrimers in cancer therapy including polyamidomiane (PAMAM), polypropylene imine (PPI), and poly-L-lysine (PLL) is the most commonly used dendrimer. The advantage of the dendrimer above is that the outermost layer will interact with the body's antibodies and reduce the toxicity of the drug.[19,20]

PAMAM dendrimers are frequently used as therapy for brain, lung, breast, ovarian, and prostate cancer.[21] PAMAM dendrimer is capable of conjugating with various antineoplastic drugs, including DOX in the form of pH-controlled DOX–PEG–PAMAM dendrimer, DOX and tamoxifen complex with G4 PAMAM dendrimer, paclitaxel linked to grafted omega-3 fatty acids PAMAM–G4–DHA dendrimer, PEGylated G5 PAMAM dendrimer complex from Imatinib (IMT), 5-FluoroUracil (FU) as aptamer conjugate with PAMAM–PEG, Docetaxel (DTX) in the form of trastuzumab-modified DTX (TZ).[8,20,22] PAMAM dendrimer can deliver doxorubicin to a triple-negative breast cancer cell line. The study showed enhanced apoptosis and significantly elevated uptake by the cancer cells.[19] Another study with colon cancer cells showed PEGylated G4 PAMAM dendrimers as carriers for piperlongumine (PL) had better cytotoxic and apoptotic abilities than piperlongumin alone in colon cancer cells.[23]

Furthermore, the PPI endrimer was synthesized using a divergent approach that had the element 1.4-diaminobutane as the nucleus. PPI is cationically charged so that it can tear the tumor membrane that has a negative charge. As a result, the drug will be able to penetrate more optimally. Effective penetration can encourage tumor cells to perform apoptosis or cell suicide. However, the risk of toxicity to healthy cells is still unavoidable in the use of this type of PPI dendrimer.[24]

Dendrimer poly-L-lysine (PLL) has amino acids to reduce drug toxicity and antiangiogenic effects for anticancer agents. PPL needs to be modified by adding a layer of PEG to reduce the effects of cations that can cause toxicity. The advantage of PLL besides being an angiogenic is the ability to deliver drugs right to cancer cells without serious effects on surrounding healthy tissue. PLL is also favored for its ability to kill cancer cells and slow the growth of cancer cells that are still developing thus preventing the severity of the cancer cells themselves.[25,26]

Cancer drugs that use dendrimers as therapeutic agents currently exist Cisplatin (Pt) which can be used as a therapy for ovarian cancer, breast cancer, bladder cancer, and brain cancer. Cisplatin shows slower release of the drug, high accumulation in tumors, and lower cytotoxicity. Another surprising plus is the effectiveness of cisplatin, which uses dendrimers as its medicinal agent on cells that have become resistant to cisplatin. Doxorubicin is a therapy for stomach cancer, ovarian cancer, and lung cancer. In both cancer drugs Hyaluronic Acid which envelops the dendrimer aims to improve the biocompatibility of the drug.[20,27] These qualities are evident in several research on various types of cancer, however, few are summarized in TABLE 1.

TABEL 1. Application of dendrimers for the treatment of various cancer

Disease	Drug	Polymer	Cell line	Outcome	Sources
Breast cancer	Doxorubicin	PAMAM	EpCAM-	Dendrimer has enhanced apoptosis and significantly elevated uptake by the cancer cells	19
	Trastuzumab	PAMAM	MCF-7, HMEC	Trastuzumab-dendrimer-fluorine is more efficient than trastuzumab alone	28
	Lapatinib (L) and fulvestrant (F)	PAMAM	MCF-7, MDA, MB-231 HER2, SK-BR	L-PAMAM and F-PAMAM are effective against different phenotype cells	29
	Lapatinib	PAMAM	HER2	PAMAM works through JNK1/2/3, ERK1/2, and HER1/2 signals as HER2-positive therapy breast cancer	30
	Cisplatin, doxorubicin	PAMAM	MCF-7, MDA-MB-231	Dendrimer improved the efficacy of drug cancer	27
Colon cancer	Piperlongumine (PL)	PAMAM	HCT 116	PL-PAMAM has greater potential cytotoxicity (of apoptosis in HCT 116 human colon cancer cells in comparison to pure PL	23
Melanoma	Paclitaxel, curcumin	PAMAM	B16F10	Dendrimer has a high potential for the formulation of hydrophobic drugs against skin cancer	31
Liver cancer	Sorafenib, Paclitaxel	PAMAM	HepG2	The antitumor and anti-metastasis efficacy of dendrimer was better than free drugs	32
Lung cancer	gefitinib (Gef) and hematoporphyrin (Hp	PAMAM	Helf, NSCLC PC-9, H1975	Dendrimer can increase intracellular reactive oxygen production, inhibit cancer cell growth, and induce cancer cell apoptosis	33
	miRNA, cis-diamine platinum (CDDP	PAMAM	H1299 and A549	Dendrimer could improve the cytotoxicity of lung cancer cell	34
Ovarian cancer	Doxorubicin	PAMAM	SK-OV-3	Dendrimer showed enhanced cytotoxicity to cancer cells and cellular uptake	35
Prostate cancer	siRNA	Amphiphilic phospholipid peptide dendrimers (AmPPDs)	CRPC PC-3	Dendrimer has more efficient intracellular uptake and endosome release of the siRNA complexes	36

Dendrimer for COVID-19

COVID-19 has become a pandemic since it was declared by WHO on March 11, 2020. This disease is caused by the SARS-CoV-2 virus. This virus is a single-standing RNA virus with S protein as the main antigen to induce the immune system. Its transmission through infectious droplets makes the transmission of this disease take place quickly. Rapid diagnosis, vaccines for long-term protection, and life-saving therapies are needed to stop pandemics.[11] The use of nanoparticles such as dendrimers is one way to improve the quality of therapy and diagnosis of COVID-19.

Dendrimers are nanoparticles that can be used as carriers for antivirals.[11] Dendrimer can also function as an antivirus. Dendrimers can interact strongly with viruses to prevent infection in the host. In HIV infection, the PPL dendrimer can block the entry of HIV by binding to the gp120 protein in the viral envelope so that binding to CD4 does not occur.[37] One of the other advantages of dendrimer is that it can be given via oral, intravenous, transdermal, topical ocular, and nasal. Intranasal administration is one of the potential dendrimers as a COVID-19 therapy because it is non-invasive and safe.[38]

Several studies on the use of dendrimers for COVID-19 therapy have been carried out both *in vitro, in vivo*, and in phase II clinical trials. OP-101, an N-acetylcysteine-conjugated PAMAM dendrimer, demonstrated in the preclinical phase the ability to activate macrophages and improve outcomes in animal models of inflammation. A study in phase II clinical trials showed that patients with severe degrees of COVID-19 who received OP-101 experienced reduced markers of neurological injury compared to the placebo group. The risk of death at 30 and 60 days after therapy was lower than placebo.[39]

miRNA therapy is one potential therapeutic modality for COVID-19. Virus miRNAs affect the immune response. Dendrimers have low transfection ability and are non-biodegradable, making them an option for carrying miRNAs. miRNAs formulated in dendrimers can be administered by inhalation or intranasally.[40]

In vivo, studies of siR-7 formed in dendrimers showed a significant reduction in viral titers and lung inflammation in experimental animals when given by inhalation.[41] A phase II clinical trial study to evaluate the efficacy and safety of aiR-7EM/KK-46, a siRNA formulated with dendrimers for the treatment of COVID-19, showed that patients who received low doses experienced a faster reduction in symptoms than the control group. Significant side effects caused by this drug were not found.[42]

SPL7013 Gel (Viva Gel) is an example of a drug for HSV2 (Herpes simplex virus type 2) and HIV (human immunodeficiency virus) using dendrimers that are available on the market. Antiviral therapy for these two viruses shows good results through the mechanism of preventing viral fusion.[43] An in vitro study using Viva Gel for COVID-19 therapy showed that Viva Gel reduced the replication of the SARS-CoV-2 virus because its active substance can bind to the spike protein of SARS-CoV-2 thereby preventing the binding of this protein to the human ACE2 protein.[44]

Dendrimer is also a potential for the development of vaccine technology. The use of dendrimers in vaccine design can be virus-like proteins (antigen expression and antigen encapsulation) or synthetic nanoparticle platforms such as DNA, RNA, and vaccine subunits.[45] Nucleic acid vaccine (mRNA vaccine) is a vaccine technique with the principle of mimicking the process of viral infection. This vaccine requires effective mRNA delivery. Dendrimers can improve the stability and efficacy of mRNA vaccines.[43] Dendrimer can also enhance antibody response-ability. Studies on Ebola and H2N2 vaccines have shown that dendrimer-carrying mRNA enhances the ability of CD8+ T cells and antibody responses.[41]

The use of dendrimers in vaccines has already been used in the Zica, H1N1, and Ebola vaccines. In this vaccine, the dendrimer is used to carry the mRNA.[45] The mRNA vaccine is one of the main vaccines against COVID-19. Several vaccine developers such as BioNTech (Germany)/Pfizer (USA) and ModernaTX use lipid nanoparticles, one of which is dendrimer, in developing their vaccines.[13]

Molecular diagnosis is the gold standard for detecting the SARS-CoV-2 virus. Research with modified HT18C6(Ag) electrode with chitosan and PAMAM dendrimer-coated silicon quantum dots (SiQDs@PAMAM) can detect the SARS-CoV-2 virus using the developed voltammetric genosensor in sputum samples.[46]

Challenge on application of dendrimer

Dendrimer use in drug delivery has several disadvantages. Firstly, dendrimers with amine-based or cation-loaded surfaces have a toxic effect on cells. This type of dendrimer can interact with the lipid bilayer membrane, thereby weakening the integrity of the membrane. This interaction causes leakage of cytolytic proteins (such as lactate dehydrogenase and luciferase) and then the cell becomes lysed. Oral administration of dendrimers sometimes causes hemolysis and disseminated intravascular coagulation.[6]

The toxicity of amine-based dendrimers, like PAMAM and PPI, depends on their surface charge.[6] Both have different toxicity patterns. In PAMAM, toxicity increased with each additional branch generation but not in PPI.[47]

The toxicity of cationic dendrimers can be completely or partially modified by modifying their surface with a negative or neutral charge.[47] Synthesis of biodegradable (neutral and anionic) dendrimers such as polyester is a solution.[47] Synthesis of biodegradable (neutral and anionic) dendrimers such as polyester is a solution. It is also possible to give a positive charge to the surface by acetylation and PEGylation.[6]

Dendrimers have rapid systemic clearance. Dendrimers with small size (G2-G4) easily pass through renal filtration. Large dendrimers are easily recognized and cleaned by the reticuloendothelial system[48] Dendrimers with amine surfaces quickly bind to the vasculature so that they are easier to clear.[47]

Methods to solve the problem are to modify the surface of the dendrimer with other molecules such as PEG. PEGylation will improve dendrimer pharmacokinetics. PEG on the dendrimer surface will form a layer that reduces opsonization and reticuloendothelial recognition. However, the modifications also increase molecular weight, decrease renal clearance, and increase circulating time. Another alternative is to design hybrid nanoparticles.[48]

Dendrimer synthesis is a long, complex, and expensive process. This process has many stages and long reactions. Technological advances can facilitate the process, such as the orthogonal coupling strategy to reduce the number of reactions required.[48]

CONCLUSION

Dendrimer has many advantages as a solution in drug delivery in cancer therapy. These nanoparticles also can improve the delivery of antiviral drugs and vaccines, improve antiviral and vaccine capabilities, and improve molecular diagnostic performance for SARS-CoV-2. The use of dendrimers can improve the quality of management of cancer and COVID-19 patients.

ACKNOWLEDGEMENT

The authors would like to express their gratitude to the Magister of

Biomedical Sciences Program, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta for their encouragement in preparing this manuscript.

REFERENCES

1. Nikalje, AP. Nanotechnology and its applications in medicine. Med Chem 2015; 5(2):081-9. https://doi.org/10.4172/2161-0444.1000247
2. Carvalho MR, Reis RL, Oliveira JM. Dendrimer nanoparticles for colorectal cancer applications. J Mater Chem B 2020; 8(6):1128-38. https://doi.org/10.1039/c9tb02289a
3. Sasi S, Joseph SK, Arian AM, Thomas S, Amrutha VU, Arya GK, *et al.* An updated review on the application of dendrimers as successful nanocarriers for brain delivery of therapeutic moieties. Int J Appl Pharm 2021; 13(1):1-9. https://doi.org/10.22159/ijap.2021v13i1.39812
4. Mittal P, Saharan A, Verma R, Altalbawy FMA, Alfaidi MA, Batiha GE, *et al.* Dendrimers: A New Race of Pharmaceutical Nanocarriers. Biomed Rest Int 2021; 2021:8844030. https://doi.org/10.1155/2021/8844030
5. Abbasi E, Aval SF, Akbarzadeh A, Milani M, Nasrabadi HT, Joo SW, *et al.* Dendrimers: synthesis, applications, and properties. Nanoscale Res Lett 2014; 9(1):247. https://doi.org/10.1186/1556-276X-9-247
6. Marques BL, Carvalho GA, Freitas EMM, Chiareli RA, Barbosa TG, Di Araújo AGP, *et al.* The role of neurogenesis in neurorepair after ischemic stroke. Semin Cell Dev Biol 2019; 95:98-110. https://doi.org/10.1016/j.semcdb.2018.12.003
7. Sherje AP, Jadhav M, Dravyakar BR, Kadam D. Dendrimers: a versatile nanocarrier for drug delivery and targeting. Int J Pharm 2018; 548(1):707-20. https://doi.org/10.1016/j.ijpharm.2018.07.030
8. Chis AA, Debora C, Morgovan C, Arseniu AM, Rus LL, Butuca A, *et al.* Applications and limitations of dendrimers in biomedicine. Moleculs 2020; 25(17):3982. https://doi.org/10.3390/molecules25173982
9. Chhikara BS, Parang K. Global Cancer Statistics 2022: the trends projection analysis. Chemical Biology Letters 2023;10(1):451.
10. Jiang P, Liang B, Zhang Z, Fan B, Zeng L, Zhou Z, *et al.* New insights into nanosystems for non-small-cell lung cancer: diagnosis and treatment. RSC Adv 2023; 13(18):19540-64. https://doi.org/10.1039/D3RA03099G
11. Bhavana V, Thakor P, Singh SB, Mehra NK. COVID-19: Pathophysiology, treatment options, nanotechnology approaches, and research agenda to combating the SARS-CoV2 pandemic. Life Sci 2020; 261:118336. https://doi.org/10.1016/j.lfs.2020.118336
12. Saravanan M, Mostafavi E, Vincent S, Negash H, Andavar R, Perumal V, *et al.* Nanotechnology-based approaches for emerging and re-emerging viruses: special emphasis on COVID-19. Microb Pathog 2021; 156:104908. https://doi.org/10.1016/j.micpath.2021.104908
13. Hasanzadeh A, Alamdaran M, Ahmadi S, Nourizadeh H, Bagherzadeh MA, Mofazzal Jahromi MA, *et al.* Nanotechnology against COVID-19: Immunization, diagnostic and therapeutic studies. J Control Release 2021; 336:354-74. https://doi.org/10.1016/j.jconrel.2021.06.036
14. Kandeel M, Al-Taher A, Park BK, Kwon HJ, Al-Nazawi M. A pilot study of the antiviral activity of anionic and cationic polyamidoamine dendrimers against the Middle East respiratory syndrome coronavirus. J Med Virol 2020; 92(9):1665-70. https://doi.org/10.1002/jmv.25928
15. Bober Z, Bartusik Aebisher

D, Aebisher D. Application of dendrimers in anticancer diagnostics and therapy. Molecules 2022; 27(10):3237. https://doi.org/10.3390/molecules27103237
16. Montané X, Bajek A, Roszkowski K, Montornés JM, Giamberini M, Roszkowski S, *et al*. Encapsulation for cancer therapy. Molecules 2020; 25(7):1605. https://doi.org/10.3390/molecules25071605
17. Navya PN, Kaphle A, Srinivas SP, Bhargava SK, Rotello VM, Daima HK. Current trends and challenges in cancer management and therapy using designer nanomaterials. Nano Converg 2019; 6(1):23. https://doi.org/10.1186/s40580-019-0193-2
18. Raj S, Khurana S, Choudhari R, Kesari KK, Kamal MA, Garg N, *et al*. Specific targeting cancer cells with nanoparticles and drug delivery in cancer therapy. Semin Cancer Biol 2021; 69:166-77. https://doi.org/10.1016/j.semcancer.2019.11.002
19. Sheikh A, Abourehab M, Tulbah A, Kesharwani P. Aptamer-grafted, cell membrane-coated dendrimer loaded with doxorubicin as a targeted nanosystem against epithelial cellular adhesion molecule (EpCAM) for triple negative breast cancer therapy. J Drug Deliv Sci Technol 2023; 86:104745. https://doi.org/10.1016/j.jddst.2023.104745
20. Janaszewska A, Lazniewska J, Trzepiński P, Marcinkowska M, Klajnert-Maculewicz B. Cytotoxicity of dendrimers. Biomolecules 2019; 9(8):330. https://doi.org/10.3390/biom9080330
21. Surekha B, Kommana NS, Dubey SK, Kumar AVP, Shukla R, Kesharwani P. PAMAM dendrimer as a talented multifunctional biomimetic nanocarrier for cancer diagnosis and therapy. Colloids Surf B Biointerfaces 2021; 204:111837. https://doi.org/10.1016/j.colsurfb.2021.111837
22. Mishra MK, Kotta K, Hali M, Wykes S, Gerard HC, Hudson AP, *et al*. PAMAM dendrimer-azithromycin conjugate nanodevices for the treatment of *Chlamydia trachomatis* infections. Nanomedicine 2011; 7(6):935-44. https://doi.org/10.1016/j.nano.2011.04.008
23. Jangid AK, Patel K, Joshi U, Patel S, Singh A, Kulhari DP, *et al*. PEGylated G4 dendrimers as a promising nanocarrier for piperlongumine delivery: synthesis, characterization, and anticancer activity. Eur Polymer J 2022; 179(31):111547. https://doi.org/10.1016/j.eurpolymj.2022.111547
24. Aso E, Martinsson I, Appelhans D, Effenberg C, Benseny-Cases N, Cladera J, *et al*. Poly(propylene imine) dendrimers with histidine-maltose shell as novel type of nanoparticles for synapse and memory protection. Nanomedicine 2019; 17:198-209. https://doi.org/10.1016/j.nano.2019.01.010
25. Chen S, Huang S, Li Y, Zhou C. Recent advances in epsilon-poly-L-lysine and L-lysine-based dendrimer synthesis, modification, and biomedical applications. Front Chem 2021; 9:659304. https://doi.org/10.3389/fchem.2021.659304
26. Gorzkiewicz M, Kopeć O, Janaszewska A, Konopka M, Pędziwiatr-Werbicka E, Tarasenko II, *et al*. Poly(lysine) dendrimers form complexes with siRNA and provide its efficient uptake by myeloid cells: model studies for therapeutic nucleic acid delivery. Int J Mol Sci 2020; 21(9):3138. https://doi.org/10.3390/ijms21093138
27. Guo XL, Kang XX, Wang YQ, Zhang XJ, Li CJ, Liu Y, *et al*. Co-delivery of cisplatin and doxorubicin by covalently conjugating with polyamidoamine dendrimer for enhanced synergistic cancer therapy. Acta Biomater 2019; 84:367-77. https://doi.org/10.1016/j.actbio.2018.12.007

28. Bartusik-Aebisher D, Chrzanowski G, Bober Z, Aebisher D. An analytical study of trastuzumab-dendrimer-fluorine drug delivery system in breast cancer therapy *in vitro*. Biomed Pharmacother 2021; 133:111053. https://doi.org/10.1016/j.biopha.2020.111053
29. Lewińska A, Wróbel K, Błoniarz D, Adamczyk-Grochala J, Wołowiec S, Wnuk M. Lapatinib- and fulvestrant-PAMAM dendrimer conjugates promote apoptosis in chemotherapy-induced senescent breast cancer cells with different receptor status. Biomater Adv 2022; 140:213047. https://doi.org/10.1016/j.bioadv.2022.213047
30. Kheraldine H, Gupta I, Alhussain H, Jabeen A, Cyprian FS, Akhtar S, *et al.* Substantial cell apoptosis provoked by naked PAMAM dendrimers in HER2-positive human breast cancer via JNK and ERK1/ERK2 signalling pathways. Comput Struct Biotechnol J 2021; 19:2881-90. https://doi.org/10.1016/j.csbj.2021.05.011
31. Thuy LT, Kang N, Choi M, Lee M, Choi JS. Dendrimeric micelles composed of polyamidoamine dendrimer-peptide-cholesterol conjugates as drug carriers for the treatment of melanoma and bacterial infection. J Ind Eng Chem 2022; 114:361-376. https://doi.org/10.1016/j.jiec.2022.07.026
32. Ma G, Du X, Zhu J, Xu F, Yu H, Li J. Multi-functionalized dendrimers for targeted co-delivery of sorafenib and paclitaxel in liver cancers. J Drug Deliv Sci Technol 2021; 63:102493. https://doi.org/10.1016/j.jddst.2021.102493
33. Zhu F, Xu L, Li X, Li Z, Wang J, Chen H, *et al.* Co-delivery of gefitinib and hematoporphyrin by aptamer-modified fluorinated dendrimer for hypoxia alleviation and enhanced synergistic chemo-photodynamic therapy of NSCLC. Eur J Pharm Sci 2021; 167:106004. https://doi.org/10.1016/j.ejps.2021.106004
34. Amreddy N, Babu A, Panneerselvam J, Srivastava A, Muralidharan R, Chen A, *et al.* Chemo-biologic combinatorial drug delivery using folate receptor-targeted dendrimer nanoparticles for lung cancer treatment. Nanomedicine 2018; 14(2):373-84. https://doi.org/10.1016/j.nano.2017.11.010
35. Lee CS, Kim TW, Kang Y, Ju Y, Ryu J, Hong H, *et al.* Targeted drug delivery nanocarriers based on hyaluronic acid-decorated dendrimer encapsulating gold nanoparticles for ovarian cancer therapy. Mater Today Chem 2022; 26:101083. https://doi.org/10.1016/j.mtchem.2022.101083
36. Dong Y, Chen Y, Zhu D, Shi K, Ma C, Zhang W, *et al.* Self-assembly of amphiphilic phospholipid peptide dendrimer-based nanovectors for effective delivery of siRNA therapeutics in prostate cancer therapy. J Control Release; 322:416-25. https://doi.org/10.1016/j.jconrel.2020.04.003
37. Itani R, Tobaiqy M, Al Faraj A. Optimizing use of theranostic nanoparticles as a life-saving strategy for treating COVID-19 patients. Theranostics 2020; 10(13):5932-42. https://doi.org/10.7150/thno.46691
38. Mignani S, Shi X, Karpus A, Lentini G, Majoral JP. Functionalized dendrimer platforms as a new forefront arsenal targeting SARS-CoV-2: an opportunity. Pharmaceutics 2021; 13(9):1513. https://doi.org/10.3390/pharmaceutics13091513
39. Gusdon AM, Faraday N, Aita JS, Kumar S, Mehta I, Choi HA, *et al.* Dendrimer nanotherapy for severe COVID-19 attenuates inflammation and neurological injury markers and improves outcomes in a phase2a clinical trial. Sci Transl Med 2022; 14(654):eabo2652. https://doi.org/10.1126/scitranslmed.abo2652
40. Panda M, Kalita E, Singh S, Kumar K, Rao A, Prajapati VK. MiRNA-SARS-

CoV-2 dialogue and prospective anti-COVID-19 therapies. Life Sci 2022; 305:120761. https://doi.org/10.1016/j.lfs.2022.120761
41. Abd Elkodous M, Olojede SO, Morsi M, El-Sayyad GS. Nanomaterial-based drug delivery systems as promising carriers for patients with COVID-19. RSC Adv 2021; 11(43):26463-80. https://doi.org/10.1039/d1ra04835j
42. Khaitov M, Nikonova A, Kofiadi I, Shilovskiy I, Smirnov V, Elisytina O, *et al*. Treatment of COVID-19 patients with a SARS-CoV-2-specific siRNA-peptide dendrimer formulation. Allergy 2023; 78(6):1639-53. https://doi.org/10.1111/all.15663
43. Asdaq SMB, Ikbal AMA, Sahu RK, Bhattacharjee B, Paul T, Deka B, *et al*. Nanotechnology integration for SARS-CoV-2 diagnosis and treatment: an approach to preventing pandemic. Nanomaterials (Basel) 2021; 11(7):1841. https://doi.org/10.3390/nano11071841
44. Paull JRA, Heery GP, Bobardt MD, Castellarnau A, Luscombe CA, Fairley JK, *et al*. Virucidal and antiviral activity of astodrimer sodium against SARS-CoV-2 *in vitro*. Antiviral Res 2021; 191:105089. https://doi.org/10.1016/j.antiviral.2021.105089
45. Zare M, Sillanpää M, Ramakrishna S. Essential role of quantum science and nanoscience in antiviral strategies for COVID-19. Mater Adv 2021; 7:2188-99. https://doi.org/10.1039/D1MA00060H
46. Farzin L, Sadjadi S, Sheini A, Mohagheghpour E. A nanoscale genosensor for early detection of COVID-19 by voltammetric determination of RNA-dependent RNA polymerase (RdRP) sequence of SARS-CoV-2 virus. Mikrochim Acta 2021; 188(4):121. https://doi.org/10.1007/s00604-021-04773-6
47. Kesharwani P, Jain K, Jain NK. Dendrimer as nanocarrier for drug delivery. Prog Polym Sci 2014; 39(2):268-307. https://doi.org/10.1016/j.progpolymsci.2013.07.005
48. Hsu HJ, Bugno J, Lee SR, Hong S. Dendrimer-based nanocarriers: a versatile platform for drug delivery. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2017; 9(1):e1409. https://doi.org/10.1002/wnan.1409