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Biopolymeric nanocarriers in cancer therapy: unleashing the potency of bioactive anticancer compounds for enhancing drug delivery

Vrushali Manoj Hadkar, [ID] [a] Chirasmita Mohanty [ID] [a] and Chinnadurai Immanuel Selvaraj [ID] *[b]

Effective cancer treatment is becoming a global concern, and recent developments in nanomedicine are essential for its treatment. Cancer is a severe metabolic syndrome that affects the human population and is a significant contributing factor to deaths globally. In science, nanotechnology offers rapidly developing delivery methods for natural bioactive compounds that are becoming increasingly prominent and can be used to treat diseases in a site-specific way. Chemotherapy and radiotherapy are conventional approaches for preventing cancer progression and have adverse effects on the human body. Many chemically synthesized drugs are used as anticancer agents, but they have several side effects; hence, they are less preferred. Medicinal plants and marine microorganisms represent a vast, mostly untapped reservoir of bioactive compounds for cancer treatment. However, they have several limitations, including nonspecific targeting, weak water solubility and limited therapeutic potential. An alternative option is the use of biopolymeric nanocarriers, which can generate effective targeted treatment therapies when conjugated with natural anticancer compounds. The present review focuses on biopolymeric nanocarriers utilizing natural sources as anticancer drugs with improved tumor-targeting efficiency. This review also covers various natural anticancer compounds, the advantages and disadvantages of natural and synthetic anticancer compounds, the problems associated with natural anticancer drugs and the advantages of biopolymeric nanocarriers over synthetic nanocarriers as drug delivery agents. This review also discusses various biopolymeric nanocarriers for enhancing the controlled delivery of anticancer compounds and the future development of nanomedicines for treating cancer.

[a]School of Biosciences and Technology, Vellore Institute of Technology (VIT), Vellore, 632014, Tamil Nadu, India

[b]Department of Genetics and Plant Breeding, VIT School of Agricultural Sciences and Advanced Learning (VAIAL), VIT, Vellore, 632014, Tamil Nadu, India. E-mail: immanuelselvaraj@vit.ac.in

Vrushali Manoj Hadkar

Vrushali Manoj Hadkar has completed her Master's in cyto-genetics, molecular biology and plant biotechnology from the Department of Botany, Ramnar-ain Ruia Autonomous College, Mumbai, Maharashtra, India. Presently, she is pursuing her PhD from Vellore Institute of Technology, Vellore, Tamil Nadu, India. She have presented in international conferences. Her research interests include biomedical research related to cancer and its therapeutics.

Chirasmita Mohanty

Chirasmita Mohanty has completed her M.Sc. in Biotech-nology and is currently pursuing PhD specializing in Medicinal Plant Biotechnology. She has published in peer-reviewed journals and presented at inter-national conferences. She aims to bridge the gap between traditional herbal medicine and modern pharmacotherapy. She is passionate about bioengineer plants for enhanced pharmaco-logical properties and drug discovery.

1. Introduction

Cell proliferation is associated with cancer genesis.[1] The following six main characteristics are considered for the progression of cancer: (1) uncontrolled cell growth and differentiation, (2) promotion of angiogenesis, (3) replicative immortality, (4) enhanced proliferation of abnormal cells, (5) inhibition of apoptosis, and (6) invasion of metastasis. Thus, targeting these molecular pathways and repairing abnormalities in cells are required to control and treat cancer.[2] Genetic instabilities and alterations occur due to the uncontrolled multiplication of normal cells. As a result, it builds up inside tissues and cells, enabling normal cells to transform into cancerous cells. The genetic variations involved are loss of function in genes involved in repairing DNA (p21, p22, p27, p51, and p53), suppressor genes for tumours (NF1, NF2, p53 and RB), oncogene-biological accelerators (RAS, RAF, Bcl-2, MYC), and genes involved in cell growth and metabolism.[3] In 2022, approximately 20 million new cases of cancer (including non-melanoma skin cancers or NMSCs) and 9.7 million cancer-related deaths (including NMSCs) were recorded. In 2022, 2.5 million new cases of lung cancer were recorded, accounting for one in eight cancer cases worldwide (12.4% of all cancer cases). Malignancies of 11.6% (female breast), 9.6% (colorectum), 7.3% (prostate), and 4.9% (stomach) were the most common malignancies diagnosed worldwide. The number of new cases of cancer per year is expected to increase from 2022 to 35 million by 2050, according to forecasts based on demographics.[4]

Various options for cancer treatment include chemotherapy, hormonal therapy, cryosurgery, brachytherapy, surgery, and chemically derived drugs.[5] Chemotherapeutic agents include DNA-interactive agents, anti-tubulin agents (*e.g.*, taxanes), antimetabolites (*e.g.*, methotrexate), and hormones.[6] Additionally, the alkylating agents used are carboplatin, cisplatin, melphalan, oxaliplatin, and cyclophosphamide (which can cause nephrotoxicity, cardiovascular toxicity, hematologic toxicity, and pulmonary and gastrointestinal toxicity); doxorubicin (which can cause cardiotoxicity); and topoisomerase inhibitors such as irinotecan (which can cause neutropenia, sensory neuropathy, and diarrhoea).[7] Some significant drawbacks of chemotherapy are resistance to the drug, recurrence of cancer, and toxicity to normal healthy cells and nontargeted tissues, which ultimately ruin the patient's quality of life. Severe adverse effects from chemotherapeutic drugs might also include restricted metastasis, quick clearance, nonspecificity, and poor absorption;[8] overcoming the difficulties of current therapy; and research into new potentially effective anticancer drugs with fewer side effects. This review highlights the role of biopolymeric nanocarriers in treating cancer, their anticancer effects on plants and marine microorganisms, and their limitations. Furthermore, this review focuses on the use of natural polymers as smart nanocarriers for the targeted administration of natural anticancer agents with controlled release.

2. Tackling cancer

The field of nanotechnology contains an excellent platform for successfully renovating cancer prevention and therapies by utilizing different nano formulations. Materials science and protein engineering improvements have led to safer and more effective nanoscale targeting approaches for cancer patients.[9] Currently, drugs using various nano-formulations and their delivery systems are increasingly used to treat cancer, and some of them have been used clinically with good results. A comparison of traditional and nanobased methods for cancer treatment is shown in Fig. 1.

Nanotechnology plays a significant role in the safer diagnosis of cancer, more effective delivery of drugs to cancer cells, and molecular targeting of tumour cells to improve the therapeutic efficacy of drugs for cancer patients. It has created a platform in which traditional technologies have yet to be able to enhance the delivery of drugs *via* novel methods and carriers.[10] Improved bioactive agent protection in a serum-rich environment, reduced conflicting effects, improved bioactive agent permeability and retention effects, prolonged bloodstream circulation, improved tumour targeting capability, and elevated release profiles are certain nanomedicine advantages.[11] The ability to add anticancer compounds to carrier molecules for the treatment of specific tumours is promising because they can target specific tumours, preventing toxic side effects on normal healthy cells and tissues.[12]

3. Plants: natural source of anticancer compounds

Since ancient times, plant bioactive compounds have been employed in medical practices. Various phytocompounds restrain the initiation and growth of cancer.[13] Plant-derived compounds are favourable options enhance treatment effectiveness in cancer patients with reduced harmful effects. Many of these phytochemicals act as effective anticancer compounds that are naturally found in plants.[14] Table 1 describes the comprehensive details of therapeutic plants, phytochemicals or derived compounds, and specific cancer suppressors.

Chinnadurai Immanuel Selvaraj

Chinnadurai Immanuel Selvaraj M.Sc. Ag (Genetics and Plant Breeding), PhD in Biotechnology is an Associate Professor and HoD (Dept of G&PB), VIT School of Agricultural Innovations and Advanced Learning, Vellore, Tamil Nadu, India. His Research interests involves identifying potential leads from traditional medicinal plants, nanotechnology involving nanocarriers for efficient drug delivery, and research on phytochemistry. He has published many international research publications and book chapters.
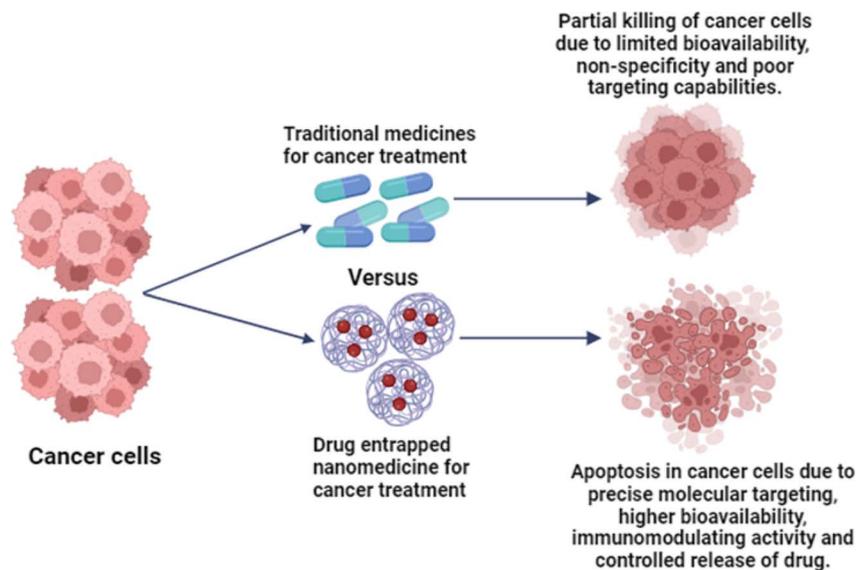
Fig. 1 Conventional and nanotechnology-based approaches for cancer therapy.

Allium sativum (liliaceae) stands out for its diverse therapeutic benefits and is a potent weapon against illnesses, including cancer and cardiovascular atherosclerosis. Its two main compounds, SACs (*S*-allylmercapto-L-cysteine and *S*-allyl-cysteine), are not only effective but also unique antioxidant compounds. SAC induces apoptosis *via* caspase activation and cell cycle arrest in the G_0/G_1 phase and upregulates the expression of the tumour suppressor protein p53 and its downstream target p21.[15] *Aloe barbadensis* (liliaceae), with its hydroxyanthraquinone known as aloe-emodin, has shown

remarkable *in vitro* and *in vivo* neuroectodermal antitumour activity, leading to apoptotic cell death. Aloe-emodin shows cytotoxic effects through apoptosis *via* a specific energy-dependent pathway involving drug incorporation.[16] Hydro-alcoholic leaf extract from *A. marmelos* (rutaceae), which contains skimmianine, has demonstrated potent antitumour activity. It was tested in Swiss albino mice with Ehrlich ascites malignancies. Leaf extracts of *A. marmelos* significantly reduced the proliferation of various cancer cell lines *in vitro* by preventing differentiation and inducing terminal erythroid

Table 1 List of therapeutic plants and their bioactive compounds effective against cancer

S. No.	Plant	Family	Phytochemicals/derived bioactive compounds	Type of cancer suppressed	References
1	*Allium sativum*	Liliaceae	Allylmercapto-L-cysteine and *S*-allylcysteine	Breast cancer	15
2	*Aloe barbadensis*	Liliaceae	Aloe-emodin	Neuroectodermal tumours	16
3	*Aegle marmelos*	Rutaceae	Skimmianine	Leukaemia and breast cancer	17
4	*Artemisia annua*	Asteraceae	Artemisinin	Breast, liver, and pancreatic cancer	18
5	*Bleekeria vitensis*	Apocynaceae	Elliptinium	Myelogenous leukaemia and breast cancer	19
6	*Chenopodium quinoa*	Amaranthaceae	Caffeic acid	Lung and colon cancer	20
7	*Combretum caffrum*	Combretaeae	Combretastatins	Leukaemia colon, and lung cancer	19
8	*Curcuma zedoaria*	Zingiberaceae	Curcumin	Colorectal cancer and skin cancer	21
9	*Glycine max*	Fabaceae	Genistein	Leukaemia	22
10	*Gossypium hirsutum*	Malvaceae	Gossypol	Colorectal cancer	23
11	*Magnolia officinalis*	Magnoliaceae	Honokiol and magnolol	Urinary bladder cancer	24
12	*Nigella sativa*	Ranunculaceae	Thymoquinone	Gastric cancer	25
13	*Oldenlandia diffusa*	Rubiaceae	Ursolic acid	Colorectal cancer	26
14	*Piper nigrum*	Piperaceae	Piperine, piperidine, piperettine	Lung cancer	27
15	*Withania somnifera*	Solanaceae	Withaferin-A	Hepatocellular carcinoma	28
16	*Musa acuminata*	Musaceae	2-Pentanone	Colorectal cancer	29
17	*Punica granatum*	Punicaceae	Punicalagin, ellagic acid	Colorectal cancer	30
18	*Psoralea corylifolia*	Leguminosae	Psoralidin	Breast, prostate, and lung cancer	31–33
19	*Salvia prionitis*	Lamiaceae	Salvicine	Lung cancer and solid tumour	34 and 35
20	*Gardenia jasminoides*	Rubiaceae	Geniposide, genipin and gardenoside	Brain tumour, oral cancer, and liver cancer	36

differentiation, including in breast cancer, melanoma, and leukemia cells.[17]

Artemisinin is a bioactive compound derived from the Chinese medicinal plant *Artemisia annua* (asteraceae). Intense activity due to the inhibition of angiogenesis, induction of apoptosis, cell cycle arrest, cancer cell migration and disruption of tumor cells *in vitro* (cancer stem cells) has been proven by *in vivo* studies.[18] Elliptinium, an ellipticine derivative, is a natural compound for treating cancer that is extracted from various parts of *Bleekeria vitensis* (apocynaceae). Elliptinium inhibits topoisomerase II, which is involved in DNA intercalation and is known to be a DNA-damaging agent that prevents the proliferation of tumour cells.[37] Caffeic acid (3,4-di-hydroxycinnamic acid) is an ester found in *Chenopodium quinoa* (amaranthaceae). In the HT-29 cell line, caffeic acid decreased cell viability with an increase in specific cell cycle alterations and caused cell death at a particular time. This mechanism of action can be attributed to the balance of pro-oxidant and antioxidant properties, prevention of reactive oxygen species (ROS) formation, inhibition of angiogenesis, enhancement of DNA oxidation, and repression of matrix metalloproteinases (an enzyme involved in invasion and metastasis).[20] The combretastins extracted from *Combretum caffrum* (combretaceae) are a family of antiangiogenic drugs that effectively inhibit the angiogenesis of new tumours. It binds to the β-subunit of tubulin at the colchicine site. This binding affects microtubule functionality, disrupting the cytoskeleton of immature endothelial cells. Combretastatin (A-4 CA4) has have been used for the treatment of colon, lung, and leukemia malignancies.[19]

Curcumin is an important compound extracted from *Curcuma zedoaria* (zingiberaceae). Curcumin modulates inflammation by inhibiting proinflammatory pathways, scavenging free radicals, promoting apoptosis, and interfering with angiogenesis. It has been demonstrated to have growth-inhibiting effects on glioblastoma cells in humans by modifying specific cellular and nuclear components and increasing the expression of genes encoding p16, p21, and p53, which are known to decrease tumour development.[21] *Glycine max* (fabaceae) naturally contains the isoflavone compound genistein. Genistein inhibits angiogenesis and arrests cancer cells at specific points, preventing uncontrolled proliferation and resulting in apoptosis. The anticancer activity of genistein was observed in a xenograft with the human leukemia cell line HL-60 in an athymic BALB/c mouse model, and a significant decrease in tumour weight was demonstrated.[22] The natural compound gossypol is present in cotton seeds of *Gossypium hirsutum* (malvaceae). Gossypol promotes apoptosis by inhibiting anti-apoptotic proteins of the BCL-2 family and triggering autophagy. Studies have revealed its anti-carcinogenic properties in various tumour types, including hematologic, lymphoid, and solid tumours. In the HCT116, HT-29, and RKO colorectal cancer cell lines, gossypol triggered autophagy and cell death.[23]

Honokiol and magnolol are bioactive compounds present in *Magnolia officinalis* (magnoliaceae). Honokiol induces apoptosis, modulates autophagy, reduces inflammation, and inhibits angiogenesis. It targets BCL-2 family proteins and balances pro-apoptotic and anti-apoptotic proteins, modulates

the PI3K/Akt pathway, inhibits nuclear factor kappa B (NF-κB), and activates adenosine monophosphate-activated protein kinase (AMPKase) whereas magnolol exhibits anti-inflammatory effects. DNA synthesis and cell proliferation in cultured cancer cell lines of the human urinary bladder were inhibited with bioactive compounds from *Magnolia officinalis* aqueous extract.[24] Thymoquinone is a bioactive compound in the seed oil of the black cumin *Nigella sativa* (ranunculaceae). It regulates cell growth, maintains tissue homeostasis, prevents uncontrolled proliferation, inhibits signal transducer and activator of transcription 3 (STAT3), disrupts the oncogenic signalling pathway, and generates ROS, which can lead to oxidative stress and cell death. Thymoquinone (10 mg kg^{-1}) reduced the size and weight of the tumours by activating apoptosis in athymic BALB/c nude mice and inhibiting the phosphorylation of STAT3 in human gastric cancer cells.[25] The natural terpene, ursolic acid, is found in *Oldenlandia diffusa* (rubiaceae). The *in vitro* study suggested that treating mouse colorectal cancer cells with ursolic acid effectively increased apoptosis and restrained cell proliferation and ROS production. Ursolic acid inhibits protein kinase B (Akt) and the mammalian target of rapamycin (mTOR) pathway, interferes with the interaction between receptor tyrosine kinases and their ligands, and affects extracellular signal-regulated kinase (ERK) signalling, influencing cell proliferation and differentiation.[26] Piperine, piperazine, piperidine, piperlongumine, and piperlonguminine are major alkaloids in *Piper nigrum* (piperaceae). Compound piperine affects the expression of cyclins, cyclin-dependent kinases (CDKs), vascular endothelial growth factor (VEGF/VEGFRs) pathway and inhibits tumour growth in tumour cell lines in mice with lung cancer and B16F-10 melanoma cells.[27] *Withania somnifera* (solanaceae) contains the steroidal lactone compound withaferin A. Oral administration of withaferin A significantly inhibited hepatocellular carcinoma and HepG2-xenografts in C57BL/6 mouse model by increasing the levels of ribosomal, S6 kinase S6 kinase (RSK), the transcription factor ELK1, death receptor 5 (DR5), and ERK and reducing the protein expression of Ki67 protein.[28] Withaferin A interacts with heat shock protein 90 (Hsp90), inhibits NF-κB, modulates ERK signalling, and affects STAT3 signalling.

Musa acuminata (musaceae), which has significant medicinal importance, contains phytocompounds, including volatile oils, phytosterols, carotenoids, biogenic amines, and phenolics commonly present in the fruit, leaf, inner trunk, flower, root, pseudo stem, and sap. A flavouring compound such as 2-pentanone found in *Musa acuminata* has shown inhibitory activity towards the cyclo-oxygenase COX-2, which helps prevent colon cancer.[29] Ellagic acid, ellagitannins, and punicalagin are among the essential polyphenols found in *Punica granatum* (punicaceae), and inhibit NF-κB, reduces inflammation, and promote apoptosis. Punicalagin from *P. granatum* juice has been shown to induce colon cancer cell (Caco-2) death in several studies. Punicalagin activates the intrinsic apoptotic pathway by downregulating apoptotic proteins like BCL-XL and activating caspase-9 and caspase-3, resulting in cell-cycle arrest.[30]

In ancient times, *Psoralea corylifolia* (leguminosae) was used to treat several ailments. It was initially distributed in Asian

regions.[38] Psoralidin is a phytocompound found in seed extracts that induces cell apoptosis in MCF-7 breast cancer cells. Psoralidin interacts with BCL-2 family proteins and affects the balance between pro-apoptotic and anti-apoptotic proteins.[31] Earlier studies have used neobavaisoflavone and psoralidin in conjunction with a TNF-related apoptosis-inducing ligand to induce apoptosis in human adenocarcinoma prostate cancer cells, thereby demonstrating anticancer activity.[32,33] Saprorthoquinone in *Salvia prionitis* had significant inhibitory effects on Lewis's lung xenograft models, the lung adenocarcinoma cell line LAX-83, the lung cancer cells A-549, and the sarcoma cell line S-180. Saprorthoquinone interacts with protein caspases and modulates proteins that control cell cycle progression.[34] This compound also showed cytotoxic activity on tumour cells resistant to multiple drugs.[35] *Gardenia jasminoides* belongs to the rubiaceae family and has abundant flavonoids that are effective at treating metabolic disorders, inflammation, and cancers. A combination of *G. jasminoides* phytoconstituents and cisplatin had a significant cytotoxic effect on the glioblastoma multiform cells U87MG and U373MG. Cisplatin displayed greater toxicity in normal astrocytes, while the phytoconstituents of *G. jasminoides* did not affect viability.[36]

4. Marine microbes: prolific source of bioactive compounds

Microorganisms are considered profound sources, including many compounds derived from secondary metabolites with therapeutic potential.[39] The marine environment is a favourable and irrepressible source of new biomolecules with important processes for healing various diseases because it contains 50% of the world's microbial biodiversity.[40] Naturally occurring products are an excellent source of bioactive compounds for preventing various cancers and an alternative option for chemically synthesized drugs.[41] There is enormous potential for discovering novel bioactive compounds from marine microorganisms that might help treat and prevent cancer.[42] Microorganisms from the sea often produce create many extremely unique and physiologically active metabolites because of their habitats, isolation, and culture conditions. Detailed information about these marine microbes, their derived bioactive compounds, and their specific cancer-suppressive effects is given in Table 2.

4.1 Marine bacteria

Dentigerumycin E is a metabolite identified in the seawater bacterial strains *Bacillus* sp. (GN1) and *Streptomyces* sp. (JB5) collected from muddy wetland shores. This compound has shown antitumour activity against breast carcinoma by generating checkpoint-inhibiting antibodies that indirectly kill cancer cells by activating the patient's immune system.[43] Exopolysaccharides and sulfated exopolysaccharides are heterogeneous polymers isolated from *Halomonas stenophila* (B100S) and present in a saline environment. Sulfated exopolysaccharides (B100S) cause the death of cancer cells.[44] Marine *Halomonas* sp. (GWS-BW-H8hM) contains the compounds

aminophenoxazinone, which has demonstrated cytotoxic activity against tumour cell lines, such as HepG2 (hepatocellular), HM02 (gastric) and MCF-7 (breast) cells. The derived bioactive compounds were 2-aminophenoxazin-3-one, 2-amino-6-hydroxyphenoxazin-3-one, and 2-amino-8-benzoyl-6-hydroxyphenoxazin-3-one.[45] Four new anthracyclines anticancer compounds were obtained from *Micromonospora* sp. (BRA006) associated with the tunicate of *Eudistoma vannamei*. The isolated compounds were 4,6,11-trihydroxy-9-propyltetracene-5,12-dione, 1-methoxy-9-propyltetracene-6,11-dione, 7,8,9,10-tetrahydro-9-hydroxy-1-methoxy-9-propyltetracene-6,11-dione, and 10β-carbomethoxy-7,8,9,10-tetrahydro-4,6,7α,9α,11-pentahydroxy-9-propyltetracene-5,12-dione. The compounds 4,6,11-trihydroxy-9-propyltetracene-5,12-dione, and 10β-carbomethoxy-7,8,9,10-tetrahydro-4,6,7α,9α,11-pentahydroxy-9-propyltetracene-5,12-dione were cytotoxic against HCT-8 colon cancer cell lines, with IC_{50} values of 12.7 μM and 6.2 μM, respectively.[46] These anthracyclines likely act by intercalating into DNA, inhibiting topoisomerase II, and generating free radicals, leading to DNA breaks and cell death.[66]

4.2 Marine actinomycetes

The bioactive compounds of the marine actinomycete *Nocardiopsis lucentensis* (strain CNR-712) were derived from lucentamycin A-D. The compounds lucentamycin A and B had shown effective *in vitro* cytotoxicity against HCT-116 colon cancer cells.[47] Isoquinoline, mansouramycin A–D, and quinones are important marine-derived compounds from *Streptomyces* sp. (Mei37) isolates. These isolated compounds were cytotoxic to various cancers. Significant cytotoxicity was observed in lung, breast, prostate, and melanoma cancer cells, evaluating the effect of these compounds as anticancer agents.[48] *Streptomyces cheonanensis* (VUK-A) strain was found in sediments of the Coringa mangrove habitat. Two physiologically active compounds (secondary metabolites) were discovered from the strain *Streptomyces cheonanensis* (VUK-A); diethyl phthalate and 2-methyl butyl propyl phthalate. The compound, 2-methyl butyl propyl phthalate was tested for cytotoxicity against cervical, breast, and ovarian cancer cell lines. The HeLa cell line showed significantly greater activity at a dose of 100 μM.[49]

Streptomyceamide C is a secondary metabolite derived from the marine *Streptomyces* sp. strain (H74-21) from sediment at a mangrove site. The cytotoxic activity of streptomyceamide C was evaluated against glioblastoma (SF-268), lung cancer (NCI-H460), and breast cancer cells (MCF-7). An IC_{50} value of 27.0 μg mL^{-1} indicated that the compound had a significant cytotoxic effect on MCF-7 cancer cells.[50] Three compounds of azalomycins F_{3a}, azalomycins F_{4a}, and azalomycins F_{5a}, as well as two novel macrocyclic lactones, azalomycin F_{4a} 2-ethyl pentyl ester and azalomycin F_{5a} 2-ethyl pentyl ester, were recovered from *Streptomyces* sp. (211726), which was found in the rhizosphere soil of mangroves. The compounds azalomycin F_{4a} 2-ethyl pentyl ester and azalomycin F_{5a} 2-ethyl pentyl ester displayed moderate cytotoxic effects against HCT-116 cells.[51]

Two novel anticancer compounds of class indolocarbazoles – streptocarbazole A and streptocarbazole B, were derived from

Table 2 An overview of several significant bioactive compounds derived from marine micro-organisms against specific cancers

S. no.	Marine microbe	Derived bioactive compound	Specific cancer supressed	References
1	**Bacteria**			
	Bacillus sp. (GN1) and *Streptomyces* sp. (JB5)	Dentigerumycin	Breast cancer	43
	Halomonas stenophila (B100)	Exopolysaccharides (EPSs) and sulphated EPSs	T-cells leukaemia	44
	Halomonas sp. (GWS-BW-H8hM)	2-Aminophenoxazin-3-one 2-Amino-6-hydroxyphenoxazin-3-one 2-Amino-8-benzoyl-6-hydroxyphenoxazin-3-one	Gastric adenocarcinoma, hepatocellular cancer, and breast cancer	45
	Micromonospora sp. (BRA006)	Anthracyclinones	Human colon adenocarcinoma	46
2	**Actinomycetes**			
	Nocardiopsis lucentensis (CNR-712)	Lucentamycins	Human colon carcinoma	47
	Streptomyces sp. (Mei37)	Mansouramycin A–D, isoquinoline, quinones	Melanoma, lung cancer, breast cancer, and prostate cancer	48
	Streptomyces cheonanensis (VUK-A)	2-Methyl butyl propyl phthalate	Breast cancer, cervical cancer, and ovarian cancer	49
	Streptomyces antibioticus (H74-21)	Streptomyceamide C	Breast cancer	50
	Streptomyces sp. (211726)	Azalomycin F5a 2-ethylpentyl ester azalomycin F4a 2-ethylpentyl ester	Colon cancer	51
	Streptomyces sp. (FMA)	Streptocarbazole A and streptocarbazole B	Leukaemia, lung cancer, and cervical cancer	52
	Streptomyces sp. (219807)	Halichoblelide D 2-Methylelaiophylin 2-Methyl-11,110 -O-dimethylelaiophylin Elaiophylin Efomycin G 11-O-Methyl-elaiophylin 11,110-O-Dimethylelaiophylin	Cervical cancer and breast cancer	53
3	**Fungi**			
	Aspergillus sp.	Asperphenin A	Human colon cancer	54
	Aspergillus glaucus (HB1-19)	Aspergiolide	Lung cancer, leukaemia, hepatocellular carcinoma	55
	Chaetomium sp. (NA-S01-R1)	Chaetovirides A, B, C and chaephilone C	Hepatocellular carcinoma and cervical cancer	56
	Halorosellinia sp. (1403) and *Guignardia* sp. (4382)	Anthracenedione	Human epidermoid carcinoma	57
	Penicillium sp. (F23-2)	Meleagrin D and E	Leukaemia	58
	Eutypella sp. (FS46)	Scopararanes H, scopararanes I, scopararane C, libertellenone A, 11-deoxydiaporthein A, diaporthein A, diaporthein B	Human glioblastoma, lung cancer and breast cancer	59
	Penicillium sclerotiorum (M-22)	Penicilazaphilones B Penicilazaphilones C	Gastric cancer and skin cancer	60
4	**Microalgae**			
	Lyngbya majuscule	Malyngamides	Colon cancer	61
	Navicula incerta	Stigmasterol	Hepatocellular carcinoma	62
	Skeletonema marinoi	Monoacylglycerides (MAGs)	Colon cancer and human myeloid leukaemia	63
	Synedra acus	Chrysolaminaran	Human colon cancer	64
	Phaeodactylum tricornutum	Nonyl 8-acetoxy-6-methyl octanoate (NAMO)	Human promyelocytic leukaemia, melanoma, and lung carcinoma	65

the marine actinomycetes *Streptomyces* sp. (FMA). The cytotoxicity of several compounds was evaluated using the A-549, HL-60, and P388 cell lines with a dose of 10 μM; compound streptocarbazole A was significantly cytotoxic to HL-60 and A-549 cell lines and arrested the cell cycle in the G$_2$/M phase for Hela cells.[52] Halichoblelide D, a compound with seven analogues were isolated from the mangrove actinomycete, *Streptomyces* sp. strain (219807). All halichoblelide compounds were evaluated through MTT assay. These compounds proved to be cytotoxic to both HeLa and MCF-7 cell lines with an IC$_{50}$ value ranging from 0.19 to 2.12 μM, respectively[53]

4.3 Marine fungi

The compound asperphenin A, a potent chemotherapeutic agent from fungus *Aspergillus* sp. was isolated for treating colon cancer cells.[54] Aspergiolide A, an anthraquinone derivative obtained from *Aspergillus glaucus* (HB1-19), marine filamentous fungus. The compound was effective against A-549, HL-60, P388 and BEL-7402 cell lines.[55] The chlorinated compounds, chaetovirides A, B, C and chaephilone C were identified from the marine-derived fungal sp. *Chaetomium* strain (NA-S01-R1). Chateoviride B and chephilone C were cytotoxic to HeLa cells and chaetoviride A towards Hep G2 cells.[56] Anthracenedione with 14 derivatives were obtained from mangrove endophytic fungi *Guignardia* sp. (4382) and *Halorosellinia* sp. (1403). Anthracenedione, compound 6 was cytotoxic to KBv200 (HeLa cell line derived) cells and KB (mouth epidermal carcinoma derived) cells, having an IC$_{50}$ values of 3.21 μM and 3.17 μM, respectively.[57]

The fungus *Penicillium* sp. (F23-2) was isolated from sediment in the deep-sea ocean using two meleagrin analogues, meleagrin D and meleagrin E, and two diketopiperazines, roquefortine H and roquefortine I. New meleagrins against lung cancer A-549 cell line showed weak cytotoxic activity. Some meleagrins compounds arrested phase G$_2$/M and led to apoptosis of HL-60 cells.[58] Pimarane-type diterpenes, scopararanes H, scopararanes I and 5 analogues of scopararane C, 11-deoxydiaporthein A, libertellenone A, diaporthein A, diaporthein B were separated from the marine fungus *Eutypella* sp. (FS46) obtained from South China Sea. The cytotoxic activity of above compounds was assessed against MCF-7, NCI–H460, and SF-268 tumour cell lines. Scopararane I showed average cytotoxic activity, and the compound diaporthein B was effective against selected tumour cell lines.[59] Penicilazaphilones B and penicilazaphilones C, two azaphilonidal derivatives found in

Penicillium sclerotiorum (M-22) marine fungus. The evaluation of these two compounds showed that penicilazaphilones B had cytotoxic activity against melanoma cells B-16 and gastric cancer cells SGC-7901 with IC$_{50}$ values 0.291 and, 0.065 mM; likewise, penicilazaphilones C was having IC$_{50}$ of 0.449 and 0.720 mM. At the same concentration, no significant cytotoxicity was shown towards normal mammary epithelial cells.[60]

4.4 Marine microalgae

Amides like bioactive compounds and malyngamides are found in marine cyanobacteria *Lyngbya majuscule*. Compound 8-*epi*-malyngamide and malyngamide C showed cytotoxicity against colon cancer cells HT29, with IC$_{50}$ values of 5.2 mM and 15.4 mM, individually.[61] Stigmasterol is an active constituent present in marine micro-algae *Navicula incerta*. The compound was screened for anticancer activity on human liver cancer cell line HepG2, showing a significant cytotoxic effect.[62] Mono-acylglycerides and their analogues were isolated from a marine diatom called *Skeletonema marinoi*. When compared to normal MePR-2B cells, these compounds demonstrated cytotoxic effect against the colon cancer cell line HCT-116 and the haematological cancer cell line U-937. The individual components of synthetic 1-monoarachidonoylglycerol were tested for their impact on U-937 and HCT-116 cells. These compounds activated caspase 3/7, leading to cause cell death.[63]

The cultured diatom alga *Synedra acus* was used to extract and characterize the 1-β-D-glucan chrysolaminaran. The isolated compound chrysolaminaran suppressed proliferation and the ability to form colonies of cells in colon cancer.[64] Among the five chemicals obtained from marine diatom *Phaeodactylum tricornutum*, the fatty alcohol ester nonyl 8-acetoxy-6-methyl octanoate (NAMO) was found. The anticancer activity of this compound was assessed for cancer cell lines; mouse melanoma B16F10, lung cancer A549, and leukaemia HL-60. Higher apoptosis was observed in HL-60 compared to other cancer cells.[65] Fig. 2 discusses phytochemicals present in plants and marine microorganisms and their therapeutic effects.

5. Advantages and disadvantages of natural and synthetic antitumour agents

Compounds derived from natural resources, including plants, sea organisms, and fungi, are used as natural anticancer
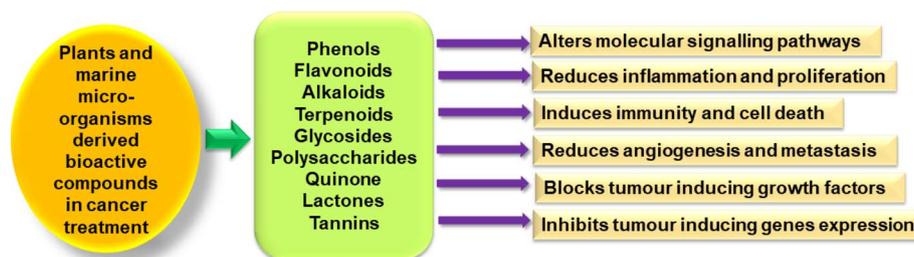

Fig. 2 Phytoconstituents from plants and marine microbes involved in cancer treatment.

Table 3 Advantages and disadvantages of natural and synthetic anticancer compounds

Sr. no.	Advantages and disadvantages	
	Natural anticancer compounds	Synthetic anticancer compounds
1	**Advantages**	
	• Natural compounds have a wide range of chemical configurations that may be able to target several pathways involved in the initiation and spread of cancer[69]	• Synthetic compounds with precise chemical structures optimised for certain targets can be developed with the potential to increase efficacy and decrease adverse reactions[74]
	• In comparison to synthetic medications, many natural compounds have lower toxicity profiles, which can lessen side effects and increase patient compliance throughout treatment. For example, it has been reported that curcumin from turmeric, is less toxic even at high dosages[70]	• Synthetic medications have a good capacity for maintenance of constant quality, purity, stability and its production than natural compounds. This is important since it ensures consistent therapeutic outcomes[75]
	• Naturally isolated compounds have the potential to work in combination with other therapies (radiation or chemotherapy) or to improve the effectiveness of traditional ones[71]	• Synthetic compounds are frequently produced after a thorough understanding of cancer biology to create medications that specifically target molecular pathways involved in the onset and spread of cancer.[74] for example, in chronic myeloid leukaemia, imatinib (Gleevec) specifically targets the BCR-ABL fusion protein[76]
	• Innovative therapeutic approaches can be facilitated by unique mechanisms of action by natural anticancer compounds which are not addressed by synthetic medications[72]	• Synthetic medications can be extended in effectiveness by optimising and modifying them to overcome resistance mechanisms that cancer cells acquire in response to therapy[77]
	• Numerous natural compounds have multitarget effects by influencing several pathways involved in the initiation and spread of cancer. For example, resveratrol, which is present in red grapes, has been reported to modify several cellular processes associated with cancer[73]	• Drug osimertinib, for example, is an epidermal growth factor (EGFR) inhibitor that is intended to target particular resistance mutations in EGFR-positive lung cancer[78]
	• The other examples include paclitaxel (taxol), berberine, curcumin *etc.*	• The other examples include doxorubicin, cyclophosphamide and cisplatin *etc.*
2	**Disadvantages**	
	• Natural compound isolation and purification can be difficult and expensive, especially when trying to get large enough quantities for medical application[79]	• Compared to natural compounds, synthetic ones might have a restricted spectrum of action, which could limit their capacity to target numerous pathways or adjust to different forms of cancer[81]
	• Different sourcing, extraction techniques, and batch variability can result in variations in the potency and purity of natural compounds, which can impact their safety and medicinal efficacy[70]	• Preclinical and clinical testing phases are necessary to assure safety and efficacy, which can make the production of synthetic drugs expensive and time-consuming[77]
	• Many naturally occurring compounds are difficult to patent, which may limit the pharmaceutical industry from turning them into commercially viable medications and thus decrease research and development expenditure[69]	• Certain synthetic medications may be more toxic than their natural counterparts, which could result in more severe side effects and less patient tolerance[75]
	• Natural compounds might contain less safety data than synthetic pharmaceuticals, including information on possible long-term effects or combinations with other treatments[70]	• Long-term safety issues with synthetic medications, such as unforeseen drug interactions or cumulative toxicities, may not become apparent until after they are used extensively in clinical settings.[82] Anthracycline chemotherapy medicines, for example, have been associated with cardiac damage, which may occur years after the treatment[83]
	• Natural compounds can sometimes cause cancer cells to become resistant to them, which reduces their efficacy as stand-alone treatments over the long run[69]	• Synthetic medicine production involves the use of chemicals and energy-intensive procedures which can have an impact on the environment by contributing to natural resource depletion and pollution.[84] For instance cyclophosphamide has been reported to cause harm to aquatic life when released into urban wastewaters (Italy)[85]
	• Certain natural compounds may become toxic when consumed in large amounts or over an extended period. For example, aristolochic acid, which is present in some traditional Chinese herbal medications, has been associated with carcinogenicity and renal damage[80]	

agents.[67] Chemically synthesised compounds using scientific procedures in laboratories are known as synthetic antitumour agents. They are designed to specifically target molecular pathways linked to the development and spread of cancer.[68] Table 3 discusses advantages and disadvantages of natural and synthetic anticancer compounds.

6. Problems associated with bioactive constituents as anti-cancer compounds: specificity and delivery

Plant and plant-derived drugs are more desirable than chemical or synthetic drugs because natural drugs are simple, safe, and less toxic, with fewer side effects. One promising option is plant-based phytochemicals and derived compounds to enhance treatment effectiveness in cancer patients and reduce unpropitious reactions.[86] Marine microorganisms-derived bioactive compounds have also presented promising anticancer activity.[87] There is an abundant source of biological diversity in the marine environment, which is the primary source of secondary metabolite production and potential utilization.[88] Numerous naturally occurring anticancer drugs have been known; however, their limited water solubility makes their formulation difficult. It takes significant proof of effectiveness from sufficient clinical studies for phytochemical anticancer medicines to be developed and approved for patients use. Some natural anticancer compounds also have drawbacks that need to be fixed before they can be used in clinical settings. Alternatively, these drawbacks should be improved for medications already being used in cancer treatment.[89] Therefore, the main drawbacks of employing phytochemicals to treat cancer include their limited therapeutic potential, poor water solubility, poor penetration into targeted cells, absorption by normal cells, and undesirable side effects.[90]

Several preclinical studies showed that the antitumour efficacy of bio-compounds from marine micro-organisms and plants is lower, indicating that combining bioactive compounds and another anticancer drug with nanocarriers is more effective than bioactive compounds alone in treating cancer. Earlier studies have been reported that polymer–drug (curcumin and doxorubicin) conjugate mixed micelles significantly inhibited

MDA-MB-231 cell growth and metastasis.[91] Even when phytochemicals are delivered in combination with chemotherapeutic medicines, the advantages are negligible because of several factors, including less solubility, low bioavailability, inability to target a diseased cell, and length of time spent targeting a cancerous cell.[92,93] Some natural compounds based anticancer drugs also have adverse side effects on the human body during and after chemotherapy.[94] The primary difficulty in co-administering phytocompounds and drugs for chemotherapy, a medication targeting specific malignant cells with minimized side effects. The limitations of the natural anticancer compounds from plants and microbes are illustrated in Fig. 3.

Doxorubicin, a chemotherapy drug causes cardiotoxicity by damaging heart muscle cells leading to heart failure and other cardiac complications. For cumulative doses between 300 mg m^{-2} and 500 mg m^{-2} (when doxorubicin is given every 3 weeks), the chance of heart damage ranges from 1%–20%.[95] It also damages white blood cells resulting in neutropenia and affects liver leading to hepatotoxicity.[96] Taxen-based drugs for instance, paclitaxel and docetaxel (plant alkaloids) can cause hypersensitivity reactions, including rash, itching, and difficulty breathing.[97] Cyclophosphamide (alkylating agent) used for the treatment of cancer with a cumulative dose of 0.75–1 gm m^{-2} over 3–6 months, affects kidney and liver function leading to nephrotoxicity and hepatotoxicity.[98] Trastuzumab (targeted therapy for HER2-positive breast cancer) leads to heart dysfunction in patients.[99] Capsaicin found in red peppers has anti-metastatic and anticancer properties sometimes lead to alopecia.[100] The estimated lethal dose capsaicin in humans is 500–5000 mg per kg of body weight.[101] The adverse effects of the natural compounds based anticancer drugs are shown in Fig. 3.

Highly organized physiological, enzymatic, and physical barriers are the main reason for nonselective tissue damage in combination treatments, which leads to limited drug partitioning with distribution to the target location. Additionally, the
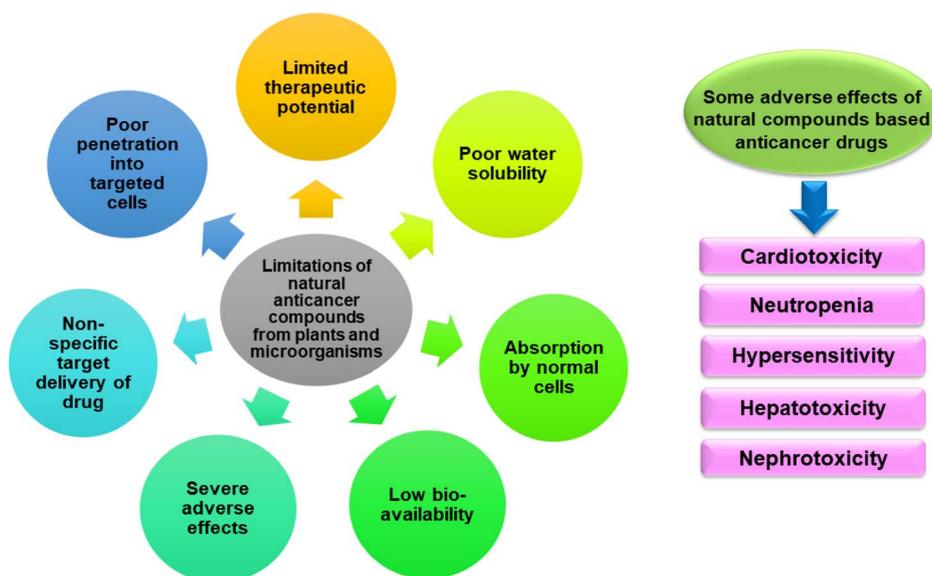

Fig. 3 Limitations and adverse effects of natural anticancer compounds.

delivery of small medicinal molecules is associated with further adverse clinical effects. Systemic toxicity and severe adverse effects can also result from variations in the pharmacological and pharmacokinetic profile of specific medicines. The development of innovative drug carriers, particularly nanotechnology-based drug carriers known as nanocarriers, has been spurred by the challenges associated with chemotherapeutic drug administration through phytochemicals.[102,103] One of the most promising approaches to treating cancer is the application of nanotechnology, which can be used to target specific molecules in cancer therapy and deliver medications to diseased cells more actively, reducing side effects in patients.[104] Polymeric nanostructured materials have been significant in diagnosing and treating diseases.[11]

7. Nanocarriers

Cancer therapies have some associated common challenges: drug resistance by tumours, the localization of the treatment to tumour sites, and limited time for drug circulation. The toxicity of antitumour drugs causes considerable complexities, including low white blood cell counts and heart problems.[9] New concepts for drug delivery can be done by repacking various bioactive compounds into multiple forms of nanometre-sized carriers. There are several ways to deliver bioactive compounds to the tumour site through nanocarriers, *viz,* delivery *via* liposomes, use of dendrimers, micelles-mediated, solid-lipid nanoparticles, and carbon nanotube-mediated drug delivery.[105]

As a novel tool for treating cancer, nanocarriers can overcome the limitations of traditional pharmaceutical delivery systems. The goal of improving the alternatives for managing malignant tumours is something that researchers are actively exploring. They have evaluated drug carriers based on nanotechnology as helpful cancer management tools, further

suggesting nano-drug carriers (10–100 nm) as unique therapeutics for cancer treatments. Different nano-drug carriers have far greater potential applications and efficacies than conventional ones for anticancer drugs.[12] Nanocarriers have some exciting features, including increased dissolution, improved bio-distribution and pharmacokinetics, toxicological prevention, and precisely targeted delivery of drugs.[106,107] Due to their nano size, they can pass through several physiological barriers, allowing the targeted malignant cell to accumulate enough medicine. This improves the drug's bioavailability and prevents adverse side effects in healthy cells. The effectiveness of the treatment increases when two or more drugs are delivered at once. Applying nanocarriers by changing their size and form allows drug administration with expected pharmacodynamic and pharmacokinetic properties.[102,108] Types of nanocarriers for delivering drugs are mentioned in Fig. 4.

Different kinds of nanocarriers have been used to deliver drugs against cancer. These consist of liposomes, dendrimers, carbon nanotubes, metallic nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, and polymeric micelles. Each of these nanocarriers offers unique advantages, such as their ability to entrap drugs and release them at the desired location.[109] Polymeric nanocarriers, for instance, encompass polymersomes, dendrimers, polymeric micelles, polymeric nanogels, and polymeric nano capsules. Lipid-based nanocarriers, on the other hand, include liposomes, solid lipid nanocarriers, phospholipid micelles, and nano emulsions. Inorganic nanocarriers, such as magnetic nanoparticles, silicon nanoparticles, gold nanoparticles, carbon nanotubes, and quantum dots, also play a significant role in drug delivery.[110] Table 4 discusses about the nanocarriers, and their advantages and limitations.

The nano-carriers mentioned above for anticancer bioactive compounds with advantages also have some limitations, such
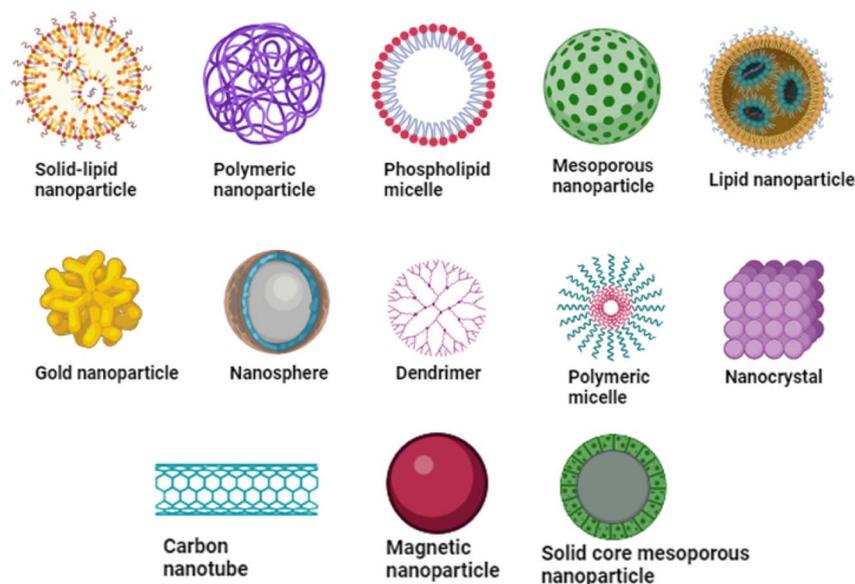

Fig. 4 Various nanocarriers for the delivery of drugs.

Table 4 The advantages and disadvantages of nanocarriers in delivery of bioactive compounds

S. no.	Nanocarriers for bioactive compounds delivery	Advantages	Limitations	References
1	Solid-lipid nanoparticles	• Encapsulation of hydrophilic and lipophilic bioactive agents • Carrier does not have toxic effects • Enhanced bioavailability of encapsulated bioactive anticancer compounds • Controlled release of drug and targeted delivery • Maintains drug stability	• Unforeseen dynamics due to polymeric changes • Agglomeration of nanoparticles • Variation in gelation tendency	111 and 112
2	Carbon nanotubes	• Permeable through biological barriers • Novel biocompatible delivery systems • Large surface area available for multiple functionalization • Production in large quantity associated with cost-effective process • Unique electrical properties • Mechanical properties reported longer stability in *in vivo* studies	• Standardization becomes difficult for a range of carbon nanotube types • Insolubility and incompatibility of material	113 and 114
3	Dendrimers	• Dendrimers shows good retention effect and permeability targets tumour cells more efficiently • They have a lower polydispersity index and enhanced entrapment of drug • Designed for applications	• Polydispersity and an extreme conjugation of bioactive compounds on surface of dendrimers • Unwanted changes in the polydispersity and material qualities • Variable correlation observed between *in vivo* studies in humans and in animal models • Difficulty associated with bio-distribution • Synthesis involves multistep and complex procedures that limit drug loading abilities	115 and 116
4	Liposomes	• Reduced toxicity • Significant activity of bioactive compounds towards intracellular and extracellular pathogens • Development and control over pharmacokinetics • Target selective properties	• Lower drug encapsulation efficiency • Intercommunications of liposomes with cells • Low shelf life and stability	117 and 118
5	Micelles	• High amount of drug loading capacity • Hydrophilic nature • Low toxic levels • Structural stability is large • Very small size	• Weak incorporation of drug • Poor extravasation • Delayed metabolic process leads to chronic liver toxicity • Complex polymer synthesis	119 and 120
6	Metallic and magnetic NPs	• Small sized (10–100 nm) to penetrate in distinct tissues through capillaries • Enhanced drug accumulation to tumour sites • Efficient diagnosis and treatment	• Low stability and biocompatibility • Possible high toxicity	121 and 122

as low stability, higher toxicity, complex synthesis process, particle size growth, low biocompatibility, and biodegradable properties. To overcome the limitations, an alternate strategy would be to create innovative nano formulations targeting tumour cells and improving the delivery of anticancer drugs with the least possible adverse effects (Table 4).

8. Natural biopolymers: best option as biocompatible and biodegradable nanocarriers

The drug administration system of the polymeric nanoparticle is an efficient substitute for the conventional drug delivery system.[123] It has actively treated various diseases and therapeutic diagnoses.[124] Polymer science is considered the fundamental backbone for the progress of new modified systems related to the delivery of drugs.[125] Polymers are divided into synthetic and natural polymers. Natural polymers have been essential in treating chronic illnesses such as cancer, diabetes, and neurological and cardiovascular problems.[126] Natural biopolymers from various sources can be employed as nanocarriers in nanomedicine applications. The importance of biopolymers for treating cancer and etiology of cancer has been discussed in Fig. 5.

Algae, microorganisms, animals, and higher plants are sources of natural biopolymers. Natural polymers like cellulose and chitosan and synthetic polymers like polyanhydrides, polyamides, polylactic acid, and polylactic-co-glycolic acid can synthesize polymeric nanocarriers.[110] Natural polymers possess various advantages over synthetic ones, including biocompatibility, non-reactivity, and non-toxicity, making them safer for targeted medication delivery (Table 5). Thus, they are often employed as excipients in pharmaceutical formulations intended for delivery via nanocarriers. They can easily have their chemical and physical structures modified to suit a variety of uses, and some of them can withstand the enzymatic breakdown processes in target cells.

8.1 Anticancer effects of natural polymers

Chitosan as a natural polymer has been reported to cause apoptosis in cancer cells via several mechanisms and inhibits the growth of new blood vessels that feed tumours, exhibiting anti-angiogenic effects. This aids in starving and slowing the growth of the tumours. A study indicated that chitosan and its derivatives have anticancer activity via antioxidant defence mechanism, apoptotic pathways and selectively penetration through the membranes of cancer cells.[168] Biopolymer fucoidan can interfere with the survival pathways of cancer cells and cause mitochondrial-mediated apoptosis, which results in cell death. Numerous mechanisms, such as the activation of caspases and the modification of BCL-2 family proteins, have been demonstrated by fucoidan to cause apoptosis in cancer cells.[169] According to studies, fucoidan inhibits the growth of cancer cells at various stages of the cell cycle, including G_0/G_1 and G_2/M.[170] Alginate inhibits the migration and invasion of cancer cells, exhibiting anti-metastatic effects. It may prevent cancer cells from adhering to extracellular matrix elements, which will hinder their capacity to spread to other locations.[171] Sulfated alginate was reported to inhibit the KSR1-dependent MEK1/ERK/mTOR signalling pathway, which facilitated autophagy and showed anticancer effects.[172] Cellulose biopolymer is one of the main ingredients in dietary fibre, and it is linked to a lower risk of colorectal cancer. Regular bowel movements help minimise the number of possible carcinogens exposed to the colon lining.[173] Starch and its derivatives have indirect effects on cancer risk or therapy, and there are possible pathways through which they might work. Specific dietary components, such as carbohydrates from whole grains and legumes, may have chemo preventive effects due to their antioxidant property and ability to influence oxidative stress and inflammation pathways.[174] Studies have indicated that pectin may have chemo preventive effects, especially against colon cancer, due to its antioxidant qualities and influence on cellular signalling pathways.[175] It has been demonstrated that hyaluronic acid inhibits angiogenesis, the process by which new blood vessels are formed to aid in the growth of tumours. This may restrict the blood flow to tumours, which would stop them from growing.[176] In vitro research has demonstrated that collagen peptides inhibit the growth of certain cancer cell lines. This impact could be caused by apoptosis induction or alteration of cell signalling pathways.[177] According to studies, albumin may prevent the migration and invasion of cancer cells, which can decrease the probability of metastasis.[178] Certain preclinical studies showed that the oral administration of xanthan gum is able to prevent tumour
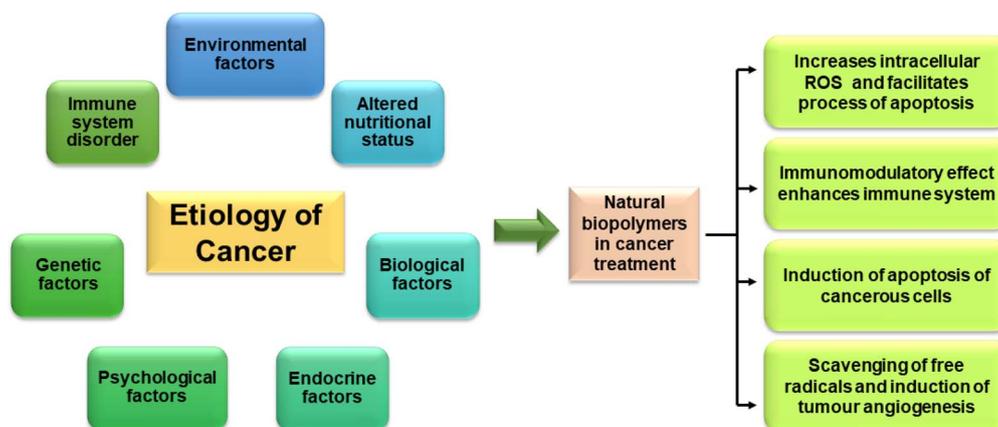

Fig. 5 Etiology of cancer and role of biopolymers in treatment of cancer.

Table 5 Characteristics and applications of natural biopolymers

Sr. No.	Natural biopolymers	Characteristics and applications	References
1	Chitosan	• A polymer composed of glucosamine and *N*-acetyl-glucosamine extracted from the outer skeleton of shellfish, such as lobster, crab, and prawns • Widely used cationic polysaccharide for drug delivery • Effective nanocarrier with long circulation duration, low immunogenicity, good serum stability, biocompatibility, and high bioavailability • Excellent option for controlled release and medication encapsulation • Decreases adverse effects of the disease	125, 127 and 128
2	Fucoidan	• Sulfated polysaccharide extracted from *Sargassum wightii*, *Dictyota dichotoma*, *Turbinaria ornata* • Precise targeting of anti-tumour cells • Helps to increase intracellular ROS and facilitates intracellular uptake of drug in the cells	129 and 130
3	Alginate	• A type of anionic linear polymer that is derived from *Laminaria hyperborean* and *Ascophyllum nodosum* • Current choice for drug delivery system • High biocompatibility, low toxicity, and mechanical stiffness • Due to absence of digestive enzymes the polymer dissolves in surrounding physiological media inside human cells	131 and 132
4	Mauran	• Sulphated polysaccharides obtained from *Halomonas maura* • Biodegradable and biocompatible • Anti-proliferative and immunomodulatory on cancer cells	133
5	Cellulose	• Plant derived polymer • Highly hydrophobic • Supresses opsonization • Helps for accumulation in target tissues	134 and 135
6	Starch	• Natural polymer with long glucose chains and large molecular weight • Enhances medication solubility, reduces toxicity levels, affordable, and biocompatible	136 and 137
7	Pectin	• Naturally occurring biopolymer consisting of α-(1–4)-D-galacturonic acid of linear polysaccharides • Absorption by pectinolytic enzymes and hydrophobic nature	138 and 139
8	Hyaluronic acid	• Natural polysaccharide found in animals • Good biocompatibility, biodegradability, and non-immunogenicity • Recognize specific receptors in cancer cells	140 and 141
9	Dextran	• Bacterial extracellular polysaccharides • Hydrophilic polysaccharide consisting of α-1,6 linked glucopyranoside residues forming a primary chain • Enhances efficacy of anticancer agents	142
10	Glucan	• Chiral polysaccharide having distinct immunological characteristics and the capacity to wrap their chiral feature supramolecularly • Highly biocompatible, soluble, superior biodegradable, and non-immunogenic with plenty of hydroxyl groups, which allow various modifications	143 and 144
11	Collagen	• Derived from fish scales, skin and bones. It is composed of three polypeptide chains, or alpha chains, coiled into a triple helix • Biocompatible, biodegradable, versatile, able to form gels for encapsulation, and shows control release properties with enhanced bioavailability	145–147
12	Albumin	• Bovine serum albumin or egg albumin. Globular water-soluble protein which is made up of single 500-amino-acid polypeptide chain folded into three structurally identical homologous domains • Biocompatible, biodegradable, enhanced pharmacokinetics and targeting potential	148–150
13	Gelatin	• A triple-helical shape protein composed of amino acids that make up gelatin, mainly glycine, proline, and hydroxyproline • Derived from collagen • Biodegradable, biocompatible, control release and enhanced drug delivery	151 and 152
14	Silk fibroin	• It is obtained from *Bombyx mori* silkworm cocoons. Being more stable, the secondary structure is made up of β-sheet crystals scattered with α-helical and random coil regions	153 and 154

Table 5 (Contd.)

Sr. No.	Natural biopolymers	Characteristics and applications	References
16	Gellan gum	• Non-immunogenic, non-toxic, encapsulated wide range of drugs, sustained release of drug, stable and target drug delivery • Natural polysaccharide from *Sphingomonas paucimobilis* bacterium composed of repeating units of glucose, glucuronic acid, and rhamnose forming linear structure	155 and 156
17	Xanthan gum	• Non-toxic, exhibit good stability, enhanced drug loading capacity • Derived from the *Xanthomonas campestris* bacterium • Composed of repeating units of glucose, mannose, and glucuronic acid • Exhibits high viscosity, controlled-release drug delivery, enhances, drug absorption, biocompatible and non-toxic	157–159
18	Casein	• Biopolymer found in bovine milk. The structure of casein is composed of peptides with hydrophilic and hydrophobic regions • Exhibits control release and stability and used for encapsulating wide range of compounds	160–162
19	Xylan	• Plant biopolymer found in hemicellulose present in cell wall of plant. It is composed of xylose units β-1,4-linked with other sugar residues • Non-toxic, targeted drug delivery and control release of drug	163–165
20	Pullulan	• Fungal biopolymer produced by *Aureobasidium pullulans* fungus. It consists of repeating malt triose units linked by α-1,6 glycosidic bonds and α-1,4 glycosidic bonds • Control release of drug and enhanced drug delivery	166 and 167

growth by modulating the pathways responsible for cancer cell proliferation and regulating the immune response.[179] A fungal biopolymer pullulan and its derivatives are reported to have anticancer activity against colon cancer.[180]

9. Biopolymeric nanocarriers for efficient drug delivery of anticancer compounds

Natural polymeric nanocarriers can effectively boost bioavailability, enhance solubility, and extend the shelf life of potential anticancer compounds, which is challenging to deliver in a controlled way (Fig. 6). Chitosan as a nanocarrier has several benefits, such as improved membrane contact, drug absorption, immune response stimulation, resistance to migration, and delayed drug release.[181] The encapsulation efficiency improved when curcumin was added to chitosan, and the loading capacity increased to 64–76%. Furthermore, chitosan nanoliposomes containing curcumin showed a significant loading in vaginal applications when compared to conventional structure.[182,183]

Fucoidan has been essential for nanotechnology-based medicine for a variety of biological uses. In addition to being an efficient therapeutic agent, fucoidan can be utilized as a nanocarrier
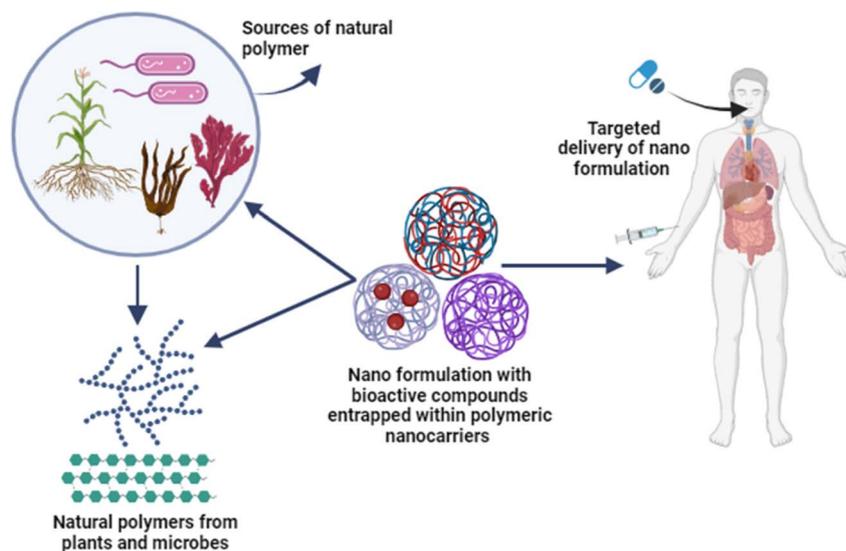

Fig. 6 Natural polymers based nano formulation for treatment of cancer.

for various medications or coupled with other cationic polymers to encapsulate diverse cargos. Ionic gelation cross-linking produces chitosan–fucoidan polymeric nanoparticles, which were then used to deliver piperlongumine. As an anticancer and antioxidant medication, the nanoparticles increased the drug's bioavailability and aqueous solubility of piperlongumine.[130]

Alginates are less toxic, highly biocompatible, and biodegradable, and they can be used as anticancer drug administration tools. In a study, the accessibility and cytotoxicity of curcumin compound in breast cancer cells were enhanced by loading it onto magnetic alginate/chitosan NCs. The results demonstrated that cells treated with NCs loaded curcumin had three to six times higher drug absorption efficiency, indicating that this nanocarrier offers a dependable way to transport medication.[184,185] The moderately halophilic bacteria *Halomonas maura* is the source of the anionic sulphated exopolysaccharide known as mauran. Because of its high sulphate concentration, it has been shown to have immunomodulatory and anticancer properties.[186] Among the most prevalent polysaccharides in nature, cellulose is an excellent option as a novel nanocarrier due to its biocompatibility and inertness. Numerous formulations applied in nanoscale forms are prepared using coatings, cellulose composites, and films.[187]

Some nanocomposites are developed as environmentally friendly nanocarriers using safe polysaccharide starch and have biodegradable properties.[136,137] Recently, curcumin conjugated with starch has been effectively delivered at the nanoscale as a bioagent. It was discovered that this composition had an acid-sensitive release profile, high loading capacity of the drug and improved colloidal stability. Additionally, due to exposure to high temperatures and UV light, the nano formulation prevented curcumin from degrading and significantly enhanced its solubility compared to free curcumin. This has been used to cure cancer, among other illnesses.[188] Essential oils can help with this issue, but their limited bioavailability is still a significant drawback. Nanoemulsifying agents are a potential solution to get around this problem. In a study, the antiproliferative effects of the essential oil of *Zataria multiflora* were investigated with a combination of citrus pectin. It was discovered that this preparation caused ROS activation, mitochondrial membrane potential damage, and arrest of the G_2/M phase, resulting in the death of breast cancer cells.[189] Hyaluronic acid helps maintain the integrity of the extracellular matrix, controls intracellular processes, and initiates and transmits cell signalling pathways linked to the start of inflammation, wound healing, tumour growth, and metastasis due to its distinct molecular makeup and physicochemical characteristics. In an earlier study, hyaluronic acid and flavonol quercetin were combined to create the flavonol quercetin-encapsulating nano system. Triple-negative 4T1 mice with highly aggressive breast cancer cells were grown *in vitro* and treated with a flavonol quercetin-encapsulated nano system. Studies conducted *in vitro* and *in vivo* revealed that the anticancer activity of the nano formulation outperformed that of flavonol quercetin.[190,191]

In previous studies, methotrexate was loaded on dextran–curcumin nano formulation to enable efficient transport into MCF-7 cells. The research indicates that the nano system achieved significant drug internalisation rates in these cells and regulated the release of methotrexate.[192] β-Glucans can come from various sources. Still, those derived from yeast and mushrooms have shown excellent immune-modulating and tumour-fighting capabilities. Interestingly, β-glucans do not directly cause death to cancer cells or tumours; instead, they activate immune cells and control the tumour microenvironment (TME), significantly reducing primary tumour growth and metastases.[193]

An extensive overview of natural biopolymers employed as nanocarriers in cancer treatment is presented in Table 6, explaining their diverse sources, associated bioactive compounds, nanostructures, and applications in targeted cancer types. Natural elements such as marine organisms, plants, and microbes can be utilized to source biopolymers that exhibit remarkable potential in biomedical applications. These biopolymers are excellent candidates for use as carriers to deliver bioactive compounds to specific locations in the body because of their low toxicity, biocompatibility, and biodegradability. When incorporated with nanotechnology, biopolymers can provide efficient solutions for cancer treatment. These biopolymers are synthesized from various natural sources, including algae, plant materials, shrimp shells, and seaweeds. The utilization of various nanostructures in conjunction with biopolymers, including dendrimers, micelles, microspheres, nanofibers, nanogels, nanoparticles, and nanovesicles, plays a pivotal role in augmenting the efficacy of drug delivery. Biopolymer-based nanocarriers encompass a broad range of therapeutic approaches, accounting for chemotherapy, gene delivery, and targeted drug delivery.

The versatile material chitosan is frequently mixed with a variety of bioactive agents, including tamoxifen, genistein, ursolic acid, curcumin diglutaric acid, and isolongifolene, to effectively target cancers of the colon, liver, ovarian, cervical, breast, and lung diseases.[196–198] These agents are typically delivered through nanomaterial formulations, such as polyethylene glycol-chitosan oligosaccharide-coated superparamagnetic iron oxide nanoparticles, lipid-polymer hybrid nanoparticles, chitosan nanoparticles, and folate-chitosan nanoparticles.[197]

Furthermore, each biopolymer's curative properties and cancer-targeting mechanisms are significantly influenced by the bioactive molecules linked to it. The biopolymer fucoidan, which comes from brown seaweeds (*Fucus vesiculosus*), has attracted a lot of interest in the field of chemotherapy because of its ability to modulate the immune system. It is incorporated into nanovesicles alongside bioactive agents such as lactoferrin, doxorubicin, and curcumin, to target pancreatic cancer; breast and melanoma cells; and colon cancer, respectively.[201,202]

Alginate, derived from brown algae (*Laminaria hyperbola*), is extensively researched for its potential in cancer treatment and targeted drug delivery systems. When combined with other polymers such as poly (D,L-lactide-*co*-glycolide) [PLGA] and chitosan, it forms microspheres or nanoparticles that encapsulate bioactive agents like curcumin, diglutaric acid, paclitaxel, and crocetin for treating colon cancer, hepatocellular cancer, and ovarian cancer, respectively.[205,207]

The selection of natural biopolymers and their corresponding nanostructures is tailored to target specific types of cancer.

Table 6 Natural biopolymers as nanocarriers in cancer therapy

Sr. no.	Natural biopolymer	Source	Bioactive agent	Nanomaterial	Application	Cancer	References
1	Chitosan	*Pandalus borealis*(shrimp), *Callinectes sapidus* (crab), *Aspergillus nidulans* (fungi)	Curcumin diglutaric acid	Polyethylene glycol–chitosan oligosaccharide-coated superparamagnetic iron oxide nanoparticles	Drug delivery	Colorectal cancer	194
			Curcumin and tamoxifen	Lipid-polymer hybrid nanoparticles	Cancer therapy, drug delivery	Liver cancer, embryonal carcinoma, ovarian cancer, lung adenocarcinoma	195
			Genistein	Chitosan nanoparticles	Targeted drug delivery	Cervical cancer	196
			Ursolic acid	Folate–chitosan nanoparticles	Drug delivery	Breast cancer	197
			Isolongifolene	Chitosan nanoparticles	Cancer therapy	Lung cancer	198
2	Fucoidan	*Fucus vesiculosus*	Fucoidan	Nanovesicle	Chemotherapy	Lung carcinoma, melanoma cells	199
			Lactoferrin	Nanoparticle	Drug delivery system	Pancreatic cancer	200
			Doxorubicin	Gold nanoparticle (DOX-Fu AuNPs)	Drug delivery and photoacoustic imaging	Breast cancer	201
			Curcumin	Mesoporous Silica nanoparticle (MSN-Cur-SS-FUC)	Nanocarrier for tumour targeting	Colon cancer	202
			Doxorubicin	Protamine Nanoparticles	Nanocarrier	Metastatic breast cancer	203
3	Alginate	*Laminaria hyperbola*	Alginate linked poly(D,L-lactide-*co*-glycolide) (PLGA)	Microspheres	Chemotherapy, targeted drug delivery	Colon cancer	204
			Curcumin diglutaric acid	Chitosan/alginate nanoparticles	Oral delivery for cancer treatment	Human epithelial colorectal adenocarcinoma	205
			Paclitaxel	Folate-targeted albumin-alginate nanoparticles	Hepatocellular cancer therapy	Human breast adenocarcinoma and human cervical cancer	206
			Crocetin	Alginate hydrogel/chitosan nanoparticle	Anticancer activity	Ovarian cancer	207
4	Mauran	*Gelidium* spp.	5-Fluorouracil	Mauran exopolysaccharide nanoparticles	Drug delivery	Breast cancer	208
			5-Fluorouracil	Chitosan nanoparticles	Cancer therapy	Glioma and breast adenocarcinoma	209
			5-Fluorouracil	Gold nanocages	Targeted drug delivery	CD133 + glioma cells	210
5	Cellulose	Plant cell wall	Cellulose acetate	Nanofibers	Drug delivery	Liver cancer	211
			Curcumin and folic acid	Nanocrystals	Therapeutic activity	Human cancer	212
6	Starch	*Zea mays*	Cisplatin	Gold nanocluster	Chemotherapeutic	Lung cancer	213

Table 6 (Contd.)

Sr. no.	Natural biopolymer	Source	Bioactive agent	Nanomaterial	Application	Cancer	References
7	Pectin	Plant cell wall	N-Acetyl-d-glucosamine	Nanoparticles	Chemotherapy, targeted drug delivery	Gastric cancer	214
			Curcumin	Citrus pectin–chitosan nanoparticles	Mucoadhesive nanoparticulate delivery system	Colon cancer	215
8	Hyaluronic acid	Umbilical cord of *Bos taurus, Sus scrofa domesticus, Ovis aries* rooster combs (*Gallus gallus domesticus*)	Hyaluronan	Micellar nanocomplexes	Targeted drug delivery	Ovarian cancer	216
			Doxorubicin	Hyaluronic acid modified Fe_3O_4 nanoparticles	Specific delivery of drug	Breast cancer	217
9	Dextran	*Leuconostoc* sp. (bacteria), yeasts	Poly(propylene imine)	Dendrimers	Chemotherapy, immunotherapy	Leukemia	218
			Methotrexate	Dextran-curcumin nanoparticles	Delivery vehicle	Breast cancer	219
10	Glucan	*Lentinula edodea* (mushroom)	1,3-β-Glucan	Curcumin encapsulated 1,3-β-glucan	Targeted drug delivery and hydrophilic	Hepatocellular carcinoma	220
11	Collagen	*Thunnus obesus* (fish scales, skin and bones)	Paclitaxel	Paclitaxel encapsulated collagen nanoparticles	Prolong release of drug	Breast cancer	221
			Doxorubicin	Doxorubicin encapsulated collagen peptide chitosan nanoparticles	Effective drug delivery and excellent biocompatibility	Cervical cancer	222
12	Albumin	Bovine serum albumin or egg albumin	Carnosic acid	Carnosic acid encapsulated albumin nanoparticles	Triggered apoptosis and significant antiproliferative action	Colon and breast cancer	223
			Piceatannol	Nanoencapsulation of piceatannol in albumin	Non-toxic and control release of drug	Colon cancer	224
13	Gelatin	*Labeo rohita* (Fish scales)	Resveratrol	Resveratrol loaded gelatin nanoparticles	Increased bioavailability and anticancer efficacy	Non-small cell lung cancer	225
			Betulinic acid	Gelatin based betulinic acid nanoparticles	Enhances bioavailability, permeability and retention effect	Different cancers	226
14	Silk fibroin	*Bombyx mori* (silkworm cocoons)	Rosmarinic acid	Rosmarinic acid-loaded silk fibroin nanoparticles	Improved anticancer potential, good biocompatibility	Cervical and breast cancer	227
			Curcumin	Curcumin-loaded Silk Fibroin nanoparticles	Biodegradable and biocompatible drug delivery	Hepatocarcinoma and neuroblastoma	228
15	Gellan gum	(*Sphingomonas elodea*) bacteria	Resveratrol	Resveratrol-loaded gellan gum-pectin nanoparticles	Better permeability and targeted release of drug	Colon cancer	229
			Paclitaxel	Gellan gum hydrogels loaded with paclitaxel	Higher anticancer activity and control release of drug	Breast cancer	230
16	Xanthan gum	*Xanthomonas campestris*	Curcumin	Xanthan gum-curcumin loaded gold nanoparticles	Enhanced permeability and biocompatibility	Lung cancer and melanoma	231
17	Poly-ferulic acid	*Triticum vulgare* bran	Paclitaxel	Paclitaxel loaded poly-ferulic acid nanoparticles	Excellent drug carrier with anticancer effects	Colon cancer	232 and 233
18	Ursolic acid	*Malus domestica*	Paclitaxel	Paclitaxel loaded ursolic acid nanoparticles	Prolonged circulation time in blood and improved anticancer efficacy	Colon cancer	234
19	Salicylic acid	*Thymus vulgaris*	Poly-salicylic acid	Prickly poly-salicylic acid nanoparticles	High biosafety, non-toxic and significant anticancer effects	Colon cancer	235 and 236

Table 6 (*Contd.*)

Sr. no.	Natural biopolymer	Source	Bioactive agent	Nanomaterial	Application	Cancer	References
20	Quercetin	*Malus domestica*	Doxorubicin	Doxorubicin loaded quercetin nanoparticles	Increased permeability and improved delivery of drug	Breast cancer	237
21	Casein	Bovine milk	Curcumin	Curcumin encapsulated casein nanoparticles	Enhanced bioavailability and toxicity	Breast cancer	238
22	Xylan	*Malus domestica*	Curcumin	Xylan-curcumin conjugated nanoparticles	Improved intracellular delivery and therapeutic efficacy of the drug	Colon cancer	239
23	Pullulan	*Aureobasidium pullulans*	Berberine	Berberine-encapsulated phenylboronic acid conjugated pullulan nanoparticles	Enhanced bioavailability and anticancer activity	Skin cancer	240

Mauran, a red algae (*Gelidium* spp) derivative, is being studied for immunotherapy in prostate cancer. It is formulated into nanogels carrageenan and 5-fluorouracil.[209] Cellulose, a natural polysaccharide in plant cell walls, has gained attention as a promising biomaterial for drug delivery systems for treatment of liver cancer.[211] Moreover, recent studies have demonstrated the therapeutic potential of nanofibers and nanocrystals loaded with curcumin and folic acid against various cancers. Maize-derived starch is used to deliver drugs for pancreatic cancer treatment *via* nanoparticles carrying amylose or gold nano-clusters containing cisplatin.[213] Pectin, a structural hetero-polysaccharide found in plant cell walls, exhibits potential utility in chemotherapy and targeted drug delivery for treating gastric cancer.[215] Specifically, nanoparticles formulated with *N*-acetyl-*d*-glucosamine or citrus pectin-chitosan hold promise for delivering bioactive agents, such as curcumin, to the desired sites of action.

The potential of hyaluronic acid-based nanocomplexes has been studied in targeted delivery and chemotherapy for ovarian and breast cancer treatment.[216] Dextran, from bacteria and yeasts, is used in leukaemia chemotherapy and immuno-therapy. It is made into nanoparticles loaded with methotrexate or curcumin.[218] Glucan, from yeasts and mushrooms, is used in nanogels for skin cancer immunotherapy and targeted drug delivery.[220] The Table 6 provides a thorough and cohesive summary of the various uses of natural biopolymers as nano-carriers in cancer therapy. It emphasises their potential to transform the therapeutic environment through efficient and tailored drug delivery systems. The nanocarriers mentioned above can be a promising option to reduce adverse effects in the human body, enhance permeability and retention effects, and control release mechanisms using bioactive compounds to prevent cancer. These natural biopolymers can encapsulate medicinal plants and marine microorganism-derived anti-cancer compounds, enhancing their delivery and improving tumour-targeting efficiency.

10. Significance and future trends

Cancer therapy can be enhanced by using nanocarriers that are specifically designed to complement the molecular and genetic characteristics of tumour. This tailoring results in more effec-tive treatment with least adverse effects. Nanocarriers can co-deliver multiple drugs concurrently, including immuno-therapy, chemotherapy and gene therapy. This makes it possible to achieve synergistic effects and may combat resis-tance mechanism that cancer cells might acquire in response to single-agent therapy. Nanocarriers can raise the influence of the amount of administered dose, by protecting bioactive compounds from enzymatic breakdown. Nanocarriers can be made to penetrate challenging biological barriers, for instance blood–brain barrier, which is essential for treating brain cancer. This broadens the array of applications and increases the range of possible uses for anticancer compounds. Nanocarrier's capacity to deliver a steady and regulated release can lower the frequency of medication delivery, enhancing patient compli-ance and quality of life. Therapeutic outcomes can be more

consistently and effectively achieved by using nanocarriers to enhance the pharmacokinetic (absorption, distribution, metabolism, and excretion) and pharmacodynamic (drug effects and processes) profiles of anticancer drugs. The tumour microenvironment (TME) poses several obstacles to the efficient administration of drugs, including low oxygen levels, acidic pH, and a thick extracellular matrix. The navigation and response of nanocarriers to various TME settings can be designed to improve medication efficacy and penetration. Advancements in nanocarrier technology and manufacturing processes can lead to affordable production techniques, making it accessible to a larger population.

Designing nanocarriers that can respond to specific stimuli within the tumour microenvironment, such as pH, temperature, and enzymes, to release anticancer compounds selectively in cancerous tissues. This will help enhance therapeutic efficacy while minimizing off-target effects. In-depth preclinical and clinical testing of nanocarrier systems to guarantee repeatability, safety, and effectiveness. Development of standard methods for assessing nanocarrier performance in diverse cancer models. Exploring the possibilities of the integration of nanocarriers in traditional cancer treatments can improve the overall outcome. Researching and implementing cost-effective production methods on a large scale, ensuring that nanomedicine therapies are accessible and affordable. Patient consent, long-term effects, and the equal distribution of advanced therapies, *etc.* encourage global collaboration and information sharing of researchers, physicians, and contributors to the industry to expedite the development and translation of nanocarrier-based cancer treatments. Integrating advanced imaging and diagnostic technology for the monitoring of the distribution, aggregation, and therapeutic reaction of nanocarrier systems in real-time, which in turn, would enable patients to make more informed treatment decisions and adjustments is one way.

Future work should also explore the production and characterization of novel natural medications from plants and microbes with better screening methods (Fig. 7). There is a need to enhance nanotherapeutic delivery systems to prevent cancer with high yield and quality using standard protocols. Although numerous bio-composite materials have been created for therapeutic usage in humans, there are still a great deal of unresolved questions and issues. Novel nano formulations with the collective combination of plant or marine microbes-based drugs with targeted therapy should be explored. The applications of bioactive compounds for cancer therapy will increase as the molecular mechanisms of treatment are better understood. Owing to the controlled release of particular drugs at predetermined locations, evaluation of drug interaction events at the tissue/cellular need to be studied. Acute and chronic investigations are necessary to evaluate the possible harm that any kind of anti-cancer therapy molecule to humans as well as the environment. Additionally, further research is needed to determine how these molecules are easily accessible. Additional *in vitro* and *in vivo* screening is necessary to evaluate the toxicity and side effects of nano-formulations. Biopolymeric nanomaterial development is still far from complete. The novel opportunities for cancer application research must be explored focusing pathways related to cancer and their mechanisms. However, the procedures related to drug delivery selection, toxicity and safety concerns of biopolymeric nanomaterials *in vitro* and *in vivo*, and their synthesis method must be thoroughly explored.
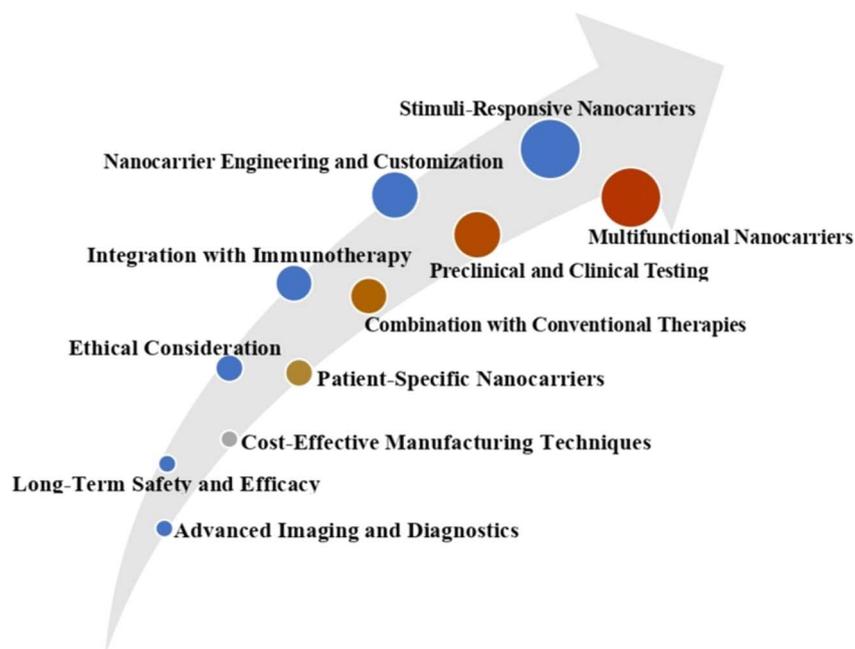

Fig. 7 Future development in the field of biopolymeric nanocarriers.

11. Conclusion

Nanomedicine and nano-delivery systems increase the ability of naturally available compounds with anticancer properties, enhancing their solubility, encapsulation, and bioavailability, decreasing their adverse side effects and toxicity. Bioactive compounds obtained in plant and marine organisms represent a significant source for discovering novel anticancer drugs used at a preventative and therapeutic level and as an alternative to chemotherapeutic drugs. Many anticancer compounds have been explored from plants and marine microorganisms, but they have difficulties related to their formulations and, therefore, have limitations for further clinical applications. The present review represented natural biopolymers as an excellent source of nanocarriers that increase the bioavailability of anticancer agents, overcome their limitations and act as biocompatible and biodegradable nanocarriers, enhancing the delivery system for curing cancer. Furthermore, if the production cost of nanoparticles is reduced, more applications will be able to benefit from their economic potential. Therefore, natural anticancer compounds-based biopolymeric nanoparticles have demonstrated significant use in enhanced drug transport capabilities, compatibility, and stability with application nanomedicine for the treatment of cancer.

Data availability

All the information was taken from already published articles, and every information contains the cited articles.

Author contributions

Vrushali Manoj Hadkar designed graphical illustrations and contributed to the writing and editing original draft; Chirasmita Mohanty contributed to the data curation, formal analysis, writing and editing original draft; Chinnadurai Immanuel Selvaraj contributed to the conceptualization, supervision, validation and editing the original draft. The authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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