

Phytochemical-Based Nanomedicine for Advanced Cancer Theranostics: Perspectives on Clinical Trials to Clinical Use

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Abstract: In the current chapter, a new strategic compilation of phytochemicals with potent antitumor properties has been addressed, most importantly focusing on cell cycle arrest and apoptotic signaling mechanism. A promising approach in tumor prevention is to eliminate cancer cells preferably via cell cycle arrest and programmed cell death with lesser harm to neighboring normal cells. Cancer cells have a survival advantage to escape apoptosis and relentlessly divide to proliferate, gearing up the cell cycle process. Recently, the use of phytochemical-derived conjugated chemotherapeutic agents has increased dramatically owing to its biocompatibility, low cytotoxicity, low resistance, and dynamic physiochemical properties discriminating normal cells in the treatment of various cancer types. For decades, biomedical investigations have targeted cell cycle and apoptotic cell death mechanism as an effective cancer-killing tool for systemically assessing the potential biological interactions of functional phytocompounds compared to its synthetic counterparts during their complete life cycles from entry, biodistribution, cellular/molecular interactions to excretion. Newly emerging nanotechnology application in anticancer drug formulations has revolutionized cancer therapy. Tissue-specific phyto-nanomedicine plays a vital role in advanced cancer diagnostics using liposome, micelle, and nanoparticles as a precise and effective delivery vehicle. This chapter specifically focuses on the therapeutic phytomolecules approved by the Food and Drug Administration (FDA, USA) along with phyto-chemopreventives currently on clinical trials (Phase-I/II/III/IV). Besides, detailed coverage is given to the FDA-approved nanotechnology-based formulations only in the areas of cancer theranostics via cell cycle arrest and apoptotic pathways including present challenges and future perspectives.

Keywords: phytochemicals, cancer therapeutics, apoptosis, cell cycle arrest, chemopreventive agents, clinical trials

Introduction

Phytochemicals have been gaining increasing attention as a promising anticancer agent, with less systemic toxicity in special relation to the regulation of cell cycle, inducing apoptosis of cancer cells, for the past few decades. Cancer has emerged as a global threat to public health along with the second major reason for death worldwide. Cancer is also called as malignancy, a population of erratically growing abnormal cells which can metastasis to other tissue organs of the body.¹ The International Agency for Research on Cancer (IARC) has released ‘GLOBOCAN 2018’ the latest global cancer burden database. According to IARC, new cancer cases rises to 18.1 million in 2018 and mortality reached 9.6 million projecting a rise of

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cancer prevalence to 23.6 million by 2030 around the world.² There are more than 100 types of cancer have been detected so far. Among all, lung, colorectal, stomach, liver, and breast cancers are the most prevalent and the foremost cause of cancer death among all cancer types, worldwide. To combat these, phytochemicals and their derivatives are either used alone, in combination with anticancer drugs or as nanomedicine formulations for better cancer theranostics over the conventional approach. Currently, plant products chiefly secondary metabolites such as phenols, alkaloids, flavonoids, flavonols, terpenoids, terpenes, steroids, etc., are among the leading source of anticancer compounds under clinical trials and clinical use.³

Apoptosis is a distinctive form of programmed cell death, a steadily regulated process, which has received remarkable attention in the field of cancer research. Apoptosis progresses through extracellular death receptor pathways as well as intracellular mitochondrial signaling pathways activating various Caspase cascades leading to cell cycle arrest and cell death.⁴ Cell growth and proliferation proceed through different phases of the cell cycle such as growth phases (G1/G2), S-phase (DNA synthesis), and M-phase (mitosis).⁵ Also, the initial G0-phase (quiescent state) awaiting the favorable time to enter the G1 phase. Cell cycle phases are regulated by binary enzyme cyclin-dependent kinases (catalytic CDKs) in interaction with regulatory cyclin subunits and further, CDKs are controlled by enzyme cyclin-dependent kinase inhibitors (CDKIs). Therefore, cancer initiation, promotion and progression can be blocked by inducing cell cycle arrest at G1/S, S/G2, and G2/M phase transition, triggering the apoptotic cell death mechanism by inactivating complex CDKs/cyclin phosphorylation.⁵ In this chapter, we have focused on two categories of phytochemicals for cancer treatment: I. DNA damage and cell cycle arrest inducing phytochemicals and II. Apoptotic phytochemicals. For example, phenyl ethyl ester, luteolin, kaempferol, vincristine, butyrate (nab), sulforaphane, lycopene, curcumin, genistein etc., induce DNA damage and cell cycle arrest at G0/G1, G2/M and G2/S phase arrest in cancer cells. Apoptosis promoting phytochemicals discussed here are irinotecan, acetoxycarvicol acetate, quercetin, piperine, curcumin, capsaicin, sanguinarine etc.

Nanotechnology is rapidly gaining global attention as an integral part of biomedical research specifically focusing on cancer diagnosis. The unique properties of nanophytochemistry are their nano-size, high surface area to

volume ratio, optical activity, surface reactivity, which enables these adsorb efficiently with phytochemicals, and chemotherapeutics for active or passive tissue-specific drug delivery. Moreover, these nanoformulations reduce systemic toxicity enhancing bioavailability with controlled and sustained release to the target site. Efficient nanocarriers used globally are liposomes, polymeric nanoparticles, polymeric micelles and nanodispersion among others.⁶ Nano-phytochemicals such as doxorubicin hydrochloride liposome, vincristine sulfate liposome, irinotecan hydrochloride liposome, paclitaxel albumin-stabilized nanoparticle formulation, paclitaxel injection concentrate for nanodispersion, docetaxel nanoparticles are amongst the FDA-approved nanoformulations for cancer therapeutics, currently in clinical use.⁶

The present chapter provides detailed knowledge of the cancer therapeutic phytochemicals approved by the Food and Drug Administration (FDA, USA) inclusive of phytochemicals currently on the clinical trials (Phase-I/II/III/IV). Besides, detailed coverage is given to the newly emerging nanotechnology-based formulations (FDA-approved) in the areas of cancer theranostics via cell cycle arrest and apoptotic pathways including present challenges and future perspectives. Finally, this chapter can provide updated knowledge of anticancer medicinal plants to the pharmaceutical companies, clinicians and researchers to explore and treat malignant tumors.

Current Status of Cancer Burden Worldwide

New cancer cases rise to 18.1 million in 2018 and mortality reached 9.6million projecting rise of cancer prevalence to 23.6 million by 2030. The International Agency for Research on Cancer (IARC) has released 'GLOBOCAN 2018' the latest global cancer burden database, which provides an estimated number of new cases diagnosed (incidents) and death (mortalities) comprising a survey of 185 countries inclusive of 36 cancer types of all sexes and all age groups combined.²

Global Cancer Burden by Population

Overall worldwide cancer patterns depict that for both sexes combined including all age groups, about 48.4% of the new cases diagnosed and more than 57.3% of the cancer mortalities occurred in Asia alone, in 2018 (Table 1). In contrast, the given data show that Africa

Table 1 Global Cancer Burden in 2018

Population	Estimated Number of New Cases in 2018	% of Incidents	Estimated Number of Mortalities in 2018	% of Mortalities
Asia	8,750,932	48.4%	5,477,064	57.3%
Africa	1,055,172	5.8%	6,93,487	7.3%
America	3,791,517	21.0%	1,371,024	20.3%
Europe	4,229,662	23.4%	1,943,478	14.6%
Oceania	2,51,674	1.4%	69,974	0.73%

Note: Estimated numbers of incidents and mortalities include both sexes and all cancer types combining all age groups worldwide.

documented with the least number of new cancer cases (5.8%) as well as the least number of mortalities (7.3%) among all populations globally. The Americas (North America, Latin America, and the Caribbean) estimated to have 21.0% of new cancer cases and 20.3% of cancer death worldwide. Although Europe has less of the total world population, it accounts for high (23.4% of incidents and 20.3% of mortalities) cancer rates. Top ten countries with the highest cancer rate including both males and females come from Europe, Oceania, and America. In contrast to other populations of the world, Oceania has the least 1.4% of cancer incident cases with fewer portions (0.73%) of cancer deaths. Asia has the highest incidents of cancer along with mortalities as it comprises of the largest population (59.76%) of the world. To further worsen the scenario, most countries suffer from poor prognosis, inadequate facilities for early diagnosis, and timely treatment to counter cancer prevalence.²

Global Cancer Burden by Type and Sex

Lung, colorectal, stomach, liver, and breast are the most frequent sites of cancer occurrence which is the foremost cause of cancer death worldwide (Figure 1). Globally, there were 2.09 million (11.6%) new cases and 1.76 million (18.4%) lung cancer deaths estimated in 2018, out of which 60.7% cancer deaths occur in Asia alone, making lungs as the topmost cancer site among all cancer types. Breast cancer is the second most diagnosed cancer (11.6%), followed by colorectal cancer (10.2%), prostate cancer (7.1%), and fifth place accounts for stomach cancer (5.7%). After lung cancer and breast cancer, colorectal cancer is the third leading cause of cancer death (9.2%), fourth stomach cancer (8.2%), and fifth liver cancer (8.2%) including both sexes and all age group. In terms of mortality by sex, breast cancer is the foremost and leading (24.2%) cause of cancer death among women,

followed by colorectal cancer (9.5%), lung cancer (8.4%), and fourth leading cervical cancer (6.6%). Male (68%) are more vulnerable to lung cancer death than females (33%), followed by liver cancer (10.2%) and stomach cancer (9.5%). Colorectal cancer (9%) and prostate cancer (6.4%) ranked fourth and fifth leading cause of cancer death in men.²

Existing Challenges in Cancer Therapeutics

Existing anticancer drugs possess severe side effects including severe damage to the surrounding normal cells, anemia due to bone marrow suppression, diarrhea/constipation, digestive tract infection, inflammation, immunosuppression, and multiorgan toxicity. The challenging feature of the cancer cell is frequent mutations and non-responsive to the prescribed drugs.³ Therefore, given the challenging circumstances of present chemotherapy, plant-based newer anticancer drugs using green and eco-friendly process is strongly demanded.

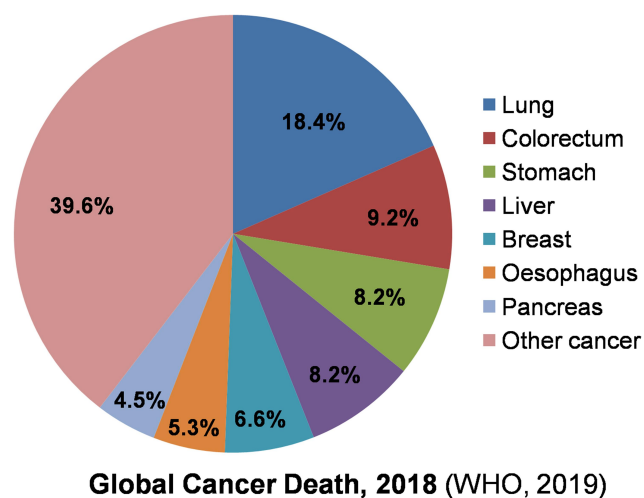


Figure 1 Percentage of global cancer deaths according to cancer types. Estimated percentages of cancer deaths include both sexes and all age groups in 2018 **Notes:** Data source: WHO, GLOBOCAN, 2018.²

Phytochemical-based anticancer drugs serve as low cost, less toxic, effective and promising against conventional chemotherapy. However, poor bioavailability, insufficient genotoxic profile, along with variable immune response creates an obstacle for its effective use in clinical trials.³ The discrepancy in various research outputs on mechanistic selectivity, allergic reactions, contaminants, drug-interactions, and safety needs to be addressed carefully before entering into the pharmaceutical market. Fully understanding anticancer drug mechanisms of action integrating experts from related/allied fields such as biology, medicine, physics, engineering, mathematics, etc., can be effective for tackling this global menace. Precise assessment of phytobioactive-drug conjugation, better bioavailability to the target tissue with advanced imaging tools to avoid over/under-diagnosis can forecast better theranostics outcomes creating a path for successful anticancer drug invention.

Cell Cycle Checkpoints: Phyto-Compound-Driven Growth Seizure versus Apoptotic Cell Death

Cell growth and proliferation proceed through different phases of the cell cycle such as growth phases (G1/G2), S-phase (DNA synthesis), and M-phase (mitosis). Also, the initial G0-phase (quiescent state) waiting a favorable time to enter the G1 phase (Figure 2). Five checkpoints of the cell cycle (represented by Red pause signs) restrict normal cell growth in response to external or internal defect stimuli. At the G0/G1 cell checkpoint, the cell returns to the G0 state on DNA damage response. At the G1/S cell checkpoint, active growth and DNA replication are ceases. At S/G2 checkpoint chromosome replication and cell division is restricted, G2/M checkpoint accounts for DNA damage seizing cell at G2 phase, and M (metaphase-mitotic spindle) checkpoints followed by irreparable DNA damage, seizing the cell from further growing, and thus compelling cancer cells to undergo programmed cell death.⁴

Programmed cell death is a steadily regulated process and a distinctive form of cell death called 'Apoptosis', which has received remarkable attention in anticancer theranostics. The induction of apoptosis is regulated by intrinsic and extrinsic signaling pathways, as once apoptosis has initiated, it inevitably ends in the death of the cell. The intrinsic apoptotic pathway is also known as the mitochondrial pathway, where mitochondria play a key role, particularly via stress stimuli like ROS (reactive

oxygen species) and RNS (reactive nitrogen species) releasing cytochrome-c by recruiting Bax and Bak proteins to the outer membrane of mitochondria.⁵ Once cytochrome-c leaks out, it binds the apoptotic factors to caspases creating apoptosome protein complex. The apoptosome activates the Caspase 3 and thereby apoptotic cell death. The extrinsic pathway is activated by extracellular tumor necrosis factor (TNF)-induced and First apoptosis signal (FAS)-ligand binding to the death receptors on cell-surface, further leads to the Caspase mediated apoptosis.⁶ In some cell types, DNA breaks into fragments and cell cycle arrests before entering apoptosis. Chemopreventives alone are highly toxic to non-cancerous cells and organs. Given in Figure 2, it demonstrates phytochemicals conjugated anticancer therapeutics can reduce cytotoxic effects to the surrounding normal cells of the tumor, initiating cell cycle arrest that leads to the cell death, hence effectively preventing tumor growth. Cell cycle checkpoints and apoptotic cell death are critically interlinked with the DNA damage/repair process, which is the central target for an effective anticancer therapeutics.^{4,6} For example, topotecan, flavopiridol, elomotecan, and exatecan mesylate anhydrous are linked with inductions of apoptosis in several human cancer such as a malignant solid tumor, ovarian and small-cell lung cancers, central nervous system tumors, acute myeloid leukemia (AML), prostate cancer and kidney cancer.⁷⁻⁹ Vinflunine ditartrate and vincristine induce apoptosis activation through G2/S and G2/M phase arrest, substantially contributing to the inhibition of cancer growth (Figure 2, Table 2). Therefore, understanding the underlying molecular mechanism, inducing cell cycle checkpoint arrest, and targeting apoptotic cellular components could be promising for the discovery of effective chemopreventives.

Phytochemicals as Cell Cycle Arrest and Apoptotic Cell Death Stimuli in Cancer Therapy

Over centuries plant-based products have been used for various medicinal purposes worldwide. In recent years, phytochemicals are being extensively explored for their potential preventive effects against cancer.¹⁰⁻¹² A wide spectrum of clinical trials has detected significant anticancer properties of various phytochemicals, which are currently in clinical use.¹³ As indicated in Figure 3, a wide array of secondary plant metabolites (phenols, alkaloids, flavonoids, flavonols, terpenoids, terpenes, steroids,

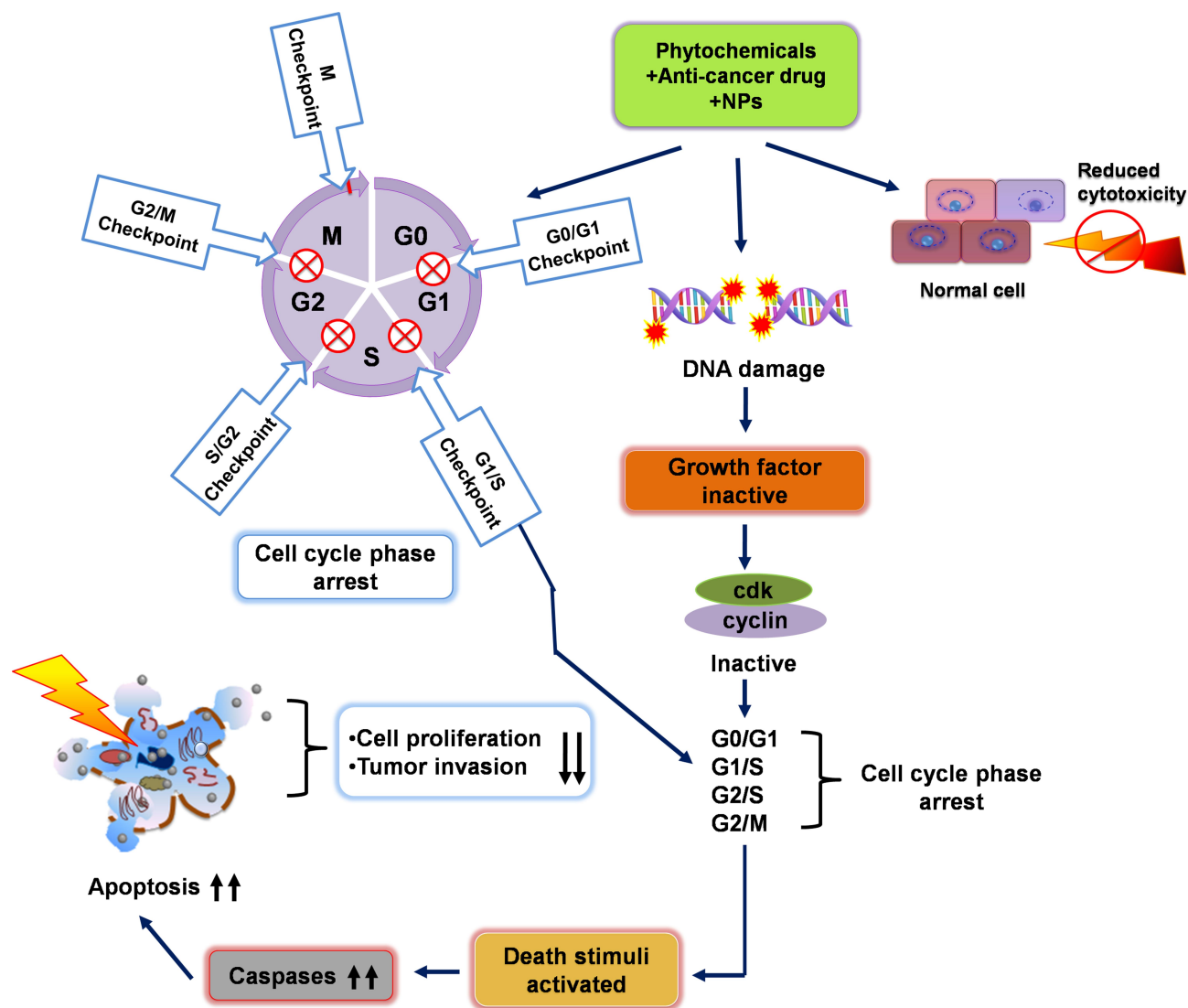
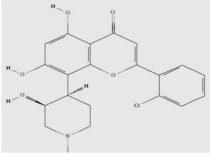
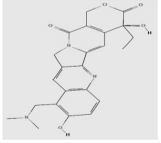
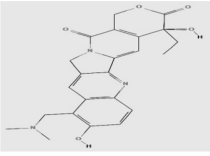
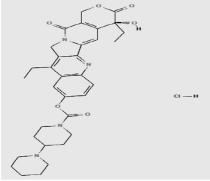
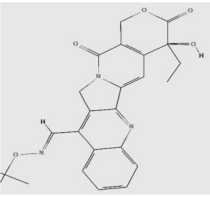


Figure 2 Phytochemicals inducing cancer cell growth arrest and cell death through cell cycle signaling checkpoint modulation. Phytochemicals induce cell cycle arrest at G0/G1 (resting phase, metabolically active), G1/S (active growth phase), S/G2 (chromosome replication and cell division), G2/M (DNA damage phase) and M (metaphase-mitotic spindle) checkpoints followed by irreparable DNA damage, seizing the cell from further growing, thus compelling cancer cells to undergo apoptosis process. **Abbreviations:** G0, Growth 0 resting phase; G1, Growth 1 active growth phase; S, Synthesis phase; G2, Growth 2 phase; M, mitotic metaphase.

flavonolignans, and organosulfur compounds) have been identified, isolated, characterized and investigated clinically for their use in cancer therapy (Figure 3). For example, phytoactive compounds such as; epigallocatechin gallate (EGCG), a polyphenol isolated from *Camellia sinensis* (Tea); genistein, a soy isoflavonoid derived from *Glycin max* Linn.; sulforaphane, an organosulfur compound from isothiocyanate class; curcumin, another polyphenol extracted from *Curcuma longa* (turmeric), and vinorelbine tartrate, from *Vinca rosea* have been proven to have potent antineoplastic efficacy against an array cancer types (Figure 3 and Table 2). Accordingly, in recent years, antineoplastic phytochemicals (eg, phenyl ethyl ester, luteolin,

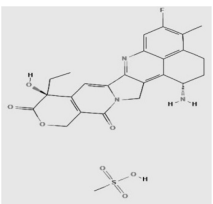
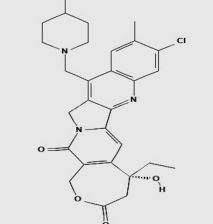
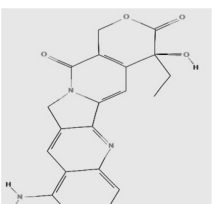
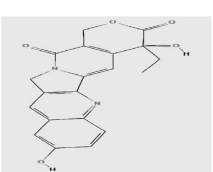
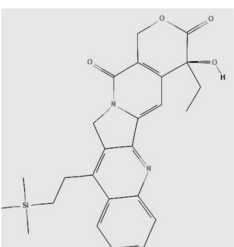
kaempferol, sulforaphane, curcumin, genistein, dioscin, resveratrol, quercetin, curcumin, and capsaicin, etc.) have been evaluated for their efficacy and safe use in cancer theranostics (Figure 3). The anticancer potency of these plant-based phytochemicals has been associated with cell cycle modulation (Figure 2) such as inhibition of cell cycle checkpoints, activation of apoptotic signaling pathways (Figure 4) as well as induction of oxidative stress, activating caspase cascades, ultimately leading to cancer cell death. Furthermore, plant-based products decrease the cytotoxicity of the chemotherapeutic agent and can be loaded with higher volume which is crucial to attaining maximal and prolonged anticancer effect.¹⁴

Table 2 Phytochemical-Based Anticancer Drugs Currently on the Market in Clinical Trials and Clinical Use as Cell Cycle Arrest and Apoptotic Agents[#]

Phytochemicals	Plant Source	Chemical Formula	Molecular Weight (g/mol)	Chemical Structure	References*
Alvocidib [Flavopiridol]	<i>Dysoxylumbinectariferum</i> (Meliaceae)	C ₂₁ H ₂₀ ClNO ₅	401.8 g/mol		[15] NCT00003256 NCT00445341 NCT00058240
Topotecan [Hycamtin]	<i>Camptothecaacuminata</i> Decne (Nyssaceae)	C ₂₃ H ₂₃ N ₃ O ₅	457.9 g/mol		[16] NCT00611468 NCT00382733 NCT01492673
Belotecan hydrochloride	<i>Camptothecaacuminata</i> Decne (Nyssaceae)	C ₂₅ H ₂₈ ClN ₃ O ₄	470 g/mol		[17] NCT00430144 NCT01497873 NCT01630018
Irinotecan HCl	<i>Camptothecaacuminata</i> Decne (Nyssaceae)	C ₃₃ H ₃₉ ClN ₄ O ₆	623.1 g/mol		[18] NCT01114555 NCT01220063 NCT00003748
Gimatecan	<i>Camptotheca acuminata</i> (Nyssaceae)	C ₂₅ H ₂₅ N ₃ O ₅	447.5 g/mol		NCT00410358 NCT00032903 NCT04029909

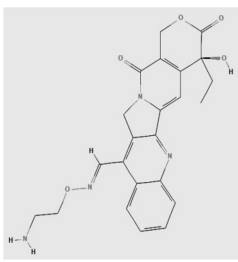
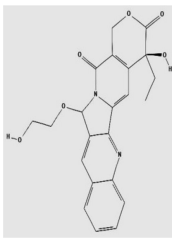
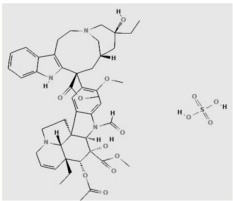
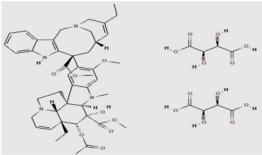
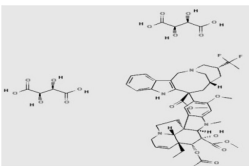
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Phytochemicals	Plant Source	Chemical Formula	Molecular Weight (g/mol)	Chemical Structure	References*
9-amino-20(S)-camptothecin [9-amino-CPT]	<i>Camptotheca acuminata</i> (Nyssaceae)	$C_{20}H_{17}N_3O_4$	363.4 g/mol		NCT00002635 NCT00003551 NCT00002671
AR-67 [10-Hydroxy Camptothecin]	<i>Camptotheca acuminata</i> (Nyssaceae)	$C_{20}H_{16}N_2O_5$	364.4 g/mol		[19,20] NCT00956787 NCT01202370 NCT00389480
Karenitecin [Cositecan]	<i>Camptotheca acuminata</i> (Nyssaceae)	$C_{25}H_{28}N_2O_4Si$	448.6 g/mol		NCT00010218 NCT00062478 NCT00477282
Exatecan mesylate anhydrous	<i>Camptotheca acuminata</i> (Nyssaceae)	$C_{25}H_{26}FN_3O_7S$	531.6 g/mol		NCT00045318 NCT00055939 NCT00005091
BN80927 [Elomotecan]	<i>Camptotheca acuminata</i> (Nyssaceae)	$C_{29}H_{32}ClN_3O_4$	558.5 g/mol		NCT01435096

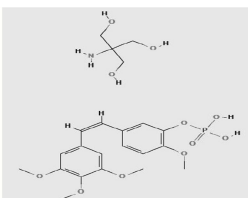
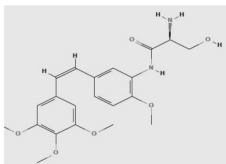
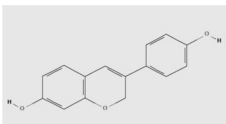
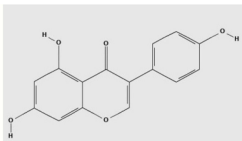
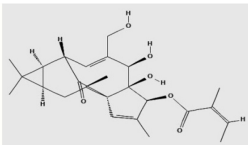
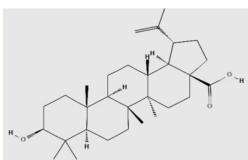
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Table 2 (Continued).

Phytochemicals	Plant Source	Chemical Formula	Molecular Weight (g/mol)	Chemical Structure	References*
Namitecan [ST-1968]	<i>Camptotheca acuminata</i> (Nyssaceae)	$C_{23}H_{22}N_4O_5$	434.4 g/mol		NCT01748019
5-(2'-Hydroxyethoxy)-20 (S)-camptothecin [DRF-1042]	<i>Camptotheca acuminata</i> (Nyssaceae)	$C_{22}H_{20}N_2O_6$	434.4 g/mol		[21]
Vincristine sulfate [Kyocristine]	<i>Vinca rosea</i> Linn. (Apocynaceae)	$C_{46}H_{58}N_4O_{14}S$	923 g/mol		[22] NCT00022555 NCT00516295
Vinorelbine tartrate	<i>Vinca rosea</i> (Apocynaceae)	$C_{53}H_{66}N_4O_{20}$	1079.1 g/mol		[23,24] NCT00432562 NCT00675597 NCT01222715
Vinflunine ditartrate [Javlor]	<i>Vinca rosea</i> (Apocynaceae)	$C_{53}H_{66}F_2N_4O_{20}$	1117.1 g/mol		[25,26] NCT00545766 NCT00284154 NCT02347332

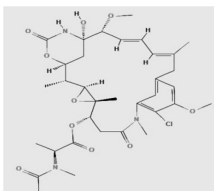
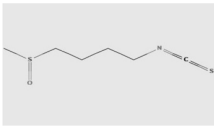
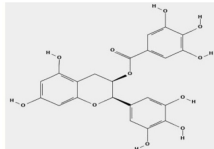
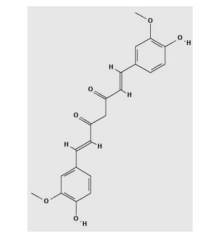
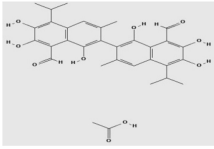
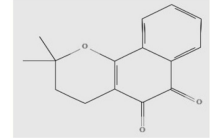
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Table 2 (Continued).

Phytochemicals	Plant Source	Chemical Formula	Molecular Weight (g/mol)	Chemical Structure	References*
Fosbretabulin tromethamine [CA4P]	<i>Combretum caffrum</i> (Combretaceae)	$C_{18}H_{19}Na_2O_8P$	517.5 g/mol		[27] NCT01305213 NCT02132468 NCT00653939
Ombrabulin [AVE8062]	<i>Combretum caffrum</i> (Combretaceae)	$C_{21}H_{26}N_2O_6$	402.4 g/mol		[28] NCT00699517 NCT01907685 NCT01263886
Idronoxil [Phenoxodiol]	<i>Glycine max</i> Linn. (Fabaceae)	$C_{15}H_{12}O_3$	240.2 g/mol		[29-31] NCT00382811 NCT00557037 NCT00382811
Genistein	<i>Glycine max</i> Linn. (Fabaceae)	$C_{15}H_{10}O_5$	270.2 g/mol		[10,32] NCT01985763 NCT01325311 NCT00244933
Ingenolmebutate [PEP 005]	<i>Euphorbia peplus</i> (Euphorbiaceae)	$C_{25}H_{34}O_6$	430.5 g/mol		[33] NCT03569345 NCT00108121 NCT02723721
Betulinic acid	<i>Betula pubescens</i> (Betulaceae)	$C_{30}H_{48}O_3$	456.7 g/mol		[34] NCT00701987

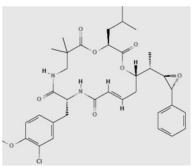
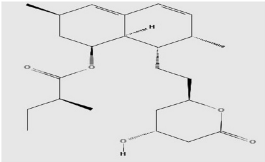
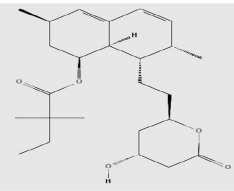
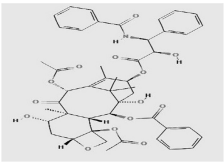
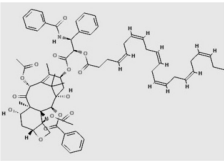
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Phytochemicals	Plant Source	Chemical Formula	Molecular Weight (g/mol)	Chemical Structure	References*
Maytansine	<i>Maytenus ovatus</i> (Celastraceae)	$C_{34}H_{46}ClN_3O_{10}$	692.2 g/mol		[35] NCT02289833 NCT00934856 NCT01641939
Sulforaphane	<i>Brassica oleracea</i> (Brassicaceae)	$C_6H_{11}NOS_2$	177.3 g/mol		[36] NCT03232138 NCT01228084 NCT02970682
Epigallocatechin gallate [EGCG]	<i>Camellia sinensis</i> (Theaceae)	$C_{22}H_{18}O_{11}$	458.4 g/mol		[37] NCT02891538 NCT02577393 NCT00459407
Curcumin	<i>Curcuma longa</i> (Zingiberaceae)	$C_{21}H_{20}O_6$	368.3 g/mol		[38] NCT01917890 NCT01160302 NCT02554344
R-(-)-Gossypol acetic acid	<i>Gossypium herbaceum</i> (Malvaceae)	$C_{32}H_{34}O_{10}$	578.6 g/mol		[39] NCT00773955 NCT00397293 NCT00666666
Beta-lapachone [ARQ 501]	<i>Tabebuia avellanedae</i> (Bignoniaceae)	$C_{15}H_{14}O_3$	242.2 g/mol		[40] NCT00524524 NCT00099190 NCT00358930

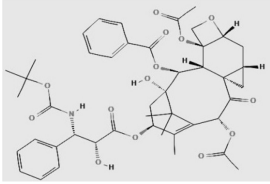
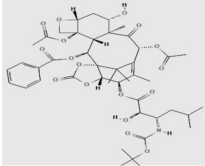
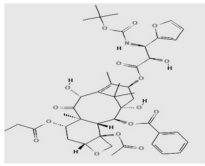
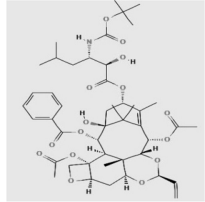
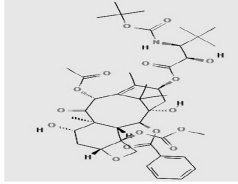
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Table 2 (Continued).

Phytochemicals	Plant Source	Chemical Formula	Molecular Weight (g/mol)	Chemical Structure	References*
Cryptophycins 52 [LY355703]	Cyanobacteria, <i>Nostoc</i> sp. [ATCC 53,789, <i>Nostoc</i> sp. GSV 224] (Nostocaceae)	$C_{36}H_{45}ClN_2O_8$	669.2 g/mol		[41,42]
Lovastatin	<i>Pleurotus ostreatus</i> (Pleurotaceae)	$C_{24}H_{36}O_5$	404.5 g/mol		NCT00462280 NCT00584012 NCT00902668
Kanglaite [Coix Seed Oil]	<i>Coix lacryma-jobi</i> (Cramineae)	NA	NA	NA	[43] NCT02553187 NCT03986528 NCT00733850
Simvastatin	<i>Aspergillus terreus</i> (Trichocomaceae)	$C_{25}H_{38}O_5$	418.5 g/mol		[44] NCT03324425 NCT00334542 NCT00944463
Paclitaxel [TAXOL]	<i>Taxus brevifolia</i> (Taxaceae)	$C_{47}H_{51}NO_{14}$	853.9 g/mol		[45]
Taxoprexin [DHA-paclitaxel]	<i>Taxus brevifolia</i> (Taxaceae)	$C_{69}H_{81}NO_{15}$	1164.3 g/mol		[46] NCT00244816 NCT00249262 NCT00243867

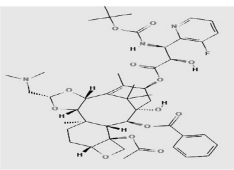
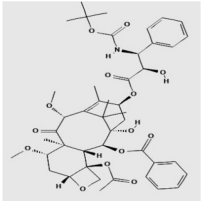
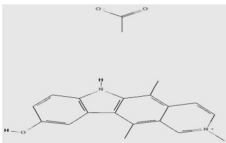
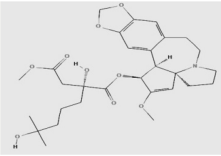
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Table 2 (Continued).

Phytochemicals	Plant Source	Chemical Formula	Molecular Weight (g/mol)	Chemical Structure	References*
Larotaxel [XRP 9881]	<i>Taxus baccata</i> L. (Taxaceae)	C ₄₅ H ₅₃ NO ₁₄	831.9 g/mol		[47] NCT00387907 NCT00417209 NCT00625664
Ortaxel [IDN-5109/BAY 59-8862]	<i>Taxus baccata</i> L. (Taxaceae)	C ₄₄ H ₅₇ NO ₁₇	871.9 g/mol		[48] NCT01989884 NCT00054314 NCT00039169
MAC 321 [Milataxel]	<i>Taxus baccata</i> L. (Taxaceae)	C ₄₄ H ₅₅ NO ₁₆	853.9 g/mol		[49] NCT00685204 NCT00063219 NCT00063427
UNII-A2VM2V569A [TPI-287]	<i>Taxus baccata</i> L. (Taxaceae)	C ₄₆ H ₆₃ NO ₁₅	869.9 g/mol		[50,51]
BMS-275,183 [Oral Taxane]	<i>Taxus baccata</i> L. (Taxaceae)	C ₄₃ H ₅₉ NO ₁₆	845.9 g/mol		NCT00103831

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Table 2 (Continued).

Phytochemicals	Plant Source	Chemical Formula	Molecular Weight (g/mol)	Chemical Structure	References*
DJ 927 [Tesetaxel]	<i>Taxus baccata</i> L. (Taxaceae)	C ₄₆ H ₆₀ FN ₃ O ₁₃	882 g/mol		[52] NCT01064713 NCT00077077 NCT01573468
Cabazitaxel [Jevtana]	<i>Taxus brevifolia</i> Nutt. (Taxaceae)	C ₄₅ H ₅₇ NO ₁₄	835.93 g/mol		[53] NCT01751308 NCT01438307 NCT01308580
Elliptinium acetate [Celpitium]	<i>Bleekeriaivitis</i> (Apocynaceae)	C ₂₀ H ₂₀ N ₂ O ₃	336.4 g/mol		[54]
Omacetaxine mepesuccinate [Synribo]	<i>Cephalotaxusharringtonia</i> var. <i>drupacea</i> (Cephalotaxaceae)	C ₂₉ H ₃₉ NO ₉	582.1 g/mol		[55] NCT00006364 NCT00462943 NCT00675350

Notes: #Source: US National Library of Medicine. *www.clinicaltrials.gov.

In recent years, combinatorial therapy is being used in clinics in which phytochemicals are used in conjunction with other chemopreventives to achieve higher cancer sensitivity compared to single drugs.^{13,14} To date, more than hundreds of phytochemicals (eg, topotecan, irinotecan HCl, vincristine sulfate, vinorelbine tartrate, vinflunine ditartrate, ingenol mebutate, maytansine, sulforaphane, curcumin, paclitaxel, etc.) have been approved by US FDA and currently, in clinical use as potent anticancer drugs,^{2,7} compiled in Table 2. Numerous clinical data suggest that these phytochemicals combat cancer via cell cycle arrest and apoptosis

with less systemic toxicity further improving human life. Further, integrating green nanotechnology into cancer science to formulate superior plant-based antineoplastic agents has become an imperative research area for pharmaceutical and biomedical sciences.^{3,10} In this section, a detailed update on antineoplastic phytochemicals, plant source, family, and their specific molecular formula along with structure is given (Table 2). Furthermore, natural anticancer phytochemicals currently under clinical trials and clinical use according to their potency through cell cycle arrest and apoptosis mechanism have been discussed.

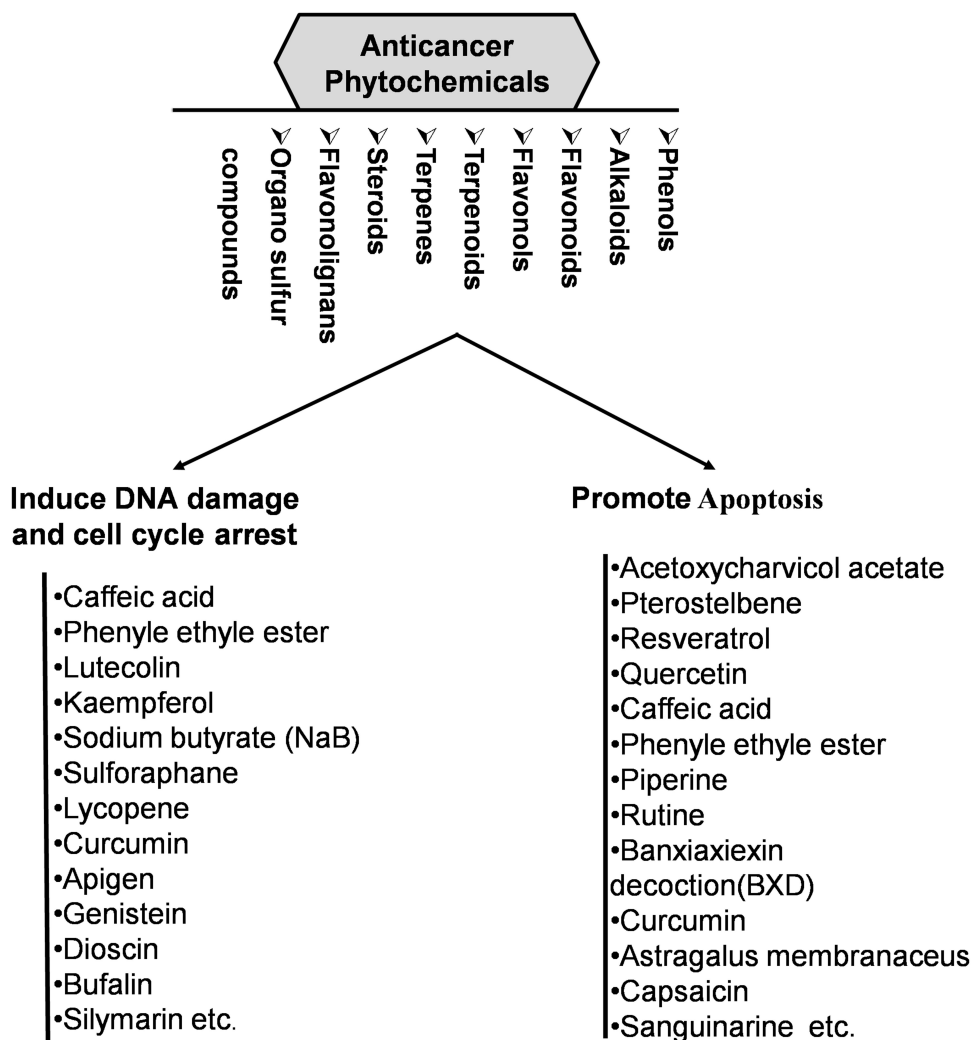


Figure 3 Anticancer phytochemicals inducing DNA damage and cell cycle growth seizure progressing apoptosis for tumor clearance.

Alvocidib [Flavopiridol]

Alvocidib is formerly known as Flavopiridol, is a flavone compound of 3-hydroxy-1-methyl piperidine chlorophenyl, extracted from Indian plant *Dysoxylum binectariferum* (Meliaceae family), with antineoplastic efficacy. It also works by inhibiting CDK9 with cyclin-dependent kinases (CDKs) inhibitor by halting phosphorylation, arresting cell cycle at G1phase, and progressing for apoptosis. A multicentre (10 institutions involved) randomized Phase II clinical trial of avlocidib followed by cytarabine and mitoxantrone (FLAM) was conducted taking 165 patients of high-risk AML (18–70 yrs) of FLAM (n = 109) and induction of 7 + 3 (n = 56). This trial resulted in increased complete response (CR) rates despite an insignificant overall survival rate (OS) and cytogenic toxicity.¹⁵ As a cell growth inhibitor and apoptosis inducer, it has been

under phase-I/II clinical trial for acute myeloid leukemia, prostate cancer, and kidney cancer treatment [NCT00003256, NCT00445341, and NCT00058240]. These ongoing clinical trials will reach to produce substantial favorable results of avlocidib enhancing AML treatment outcomes.

Topotecan [Hycamtin]

Topotecan (Hycamtin) is a camptothecin analog extracted from the tree *Camptotheca acuminata* Decne (Nyssaceae) bark and is a topoisomerase-I inhibitor. This drug is used as an antineoplastic agent and has been approved by the FDA for the treatment of ovarian cancer (1996), cervical cancer (2006), and small cell lung cancer (2007). Recently, 398 studies have been registered under US Govt. clinical trial for various cancer therapy.¹⁶ In physiological ambiance, topotecan with its active lactone form interpolate with

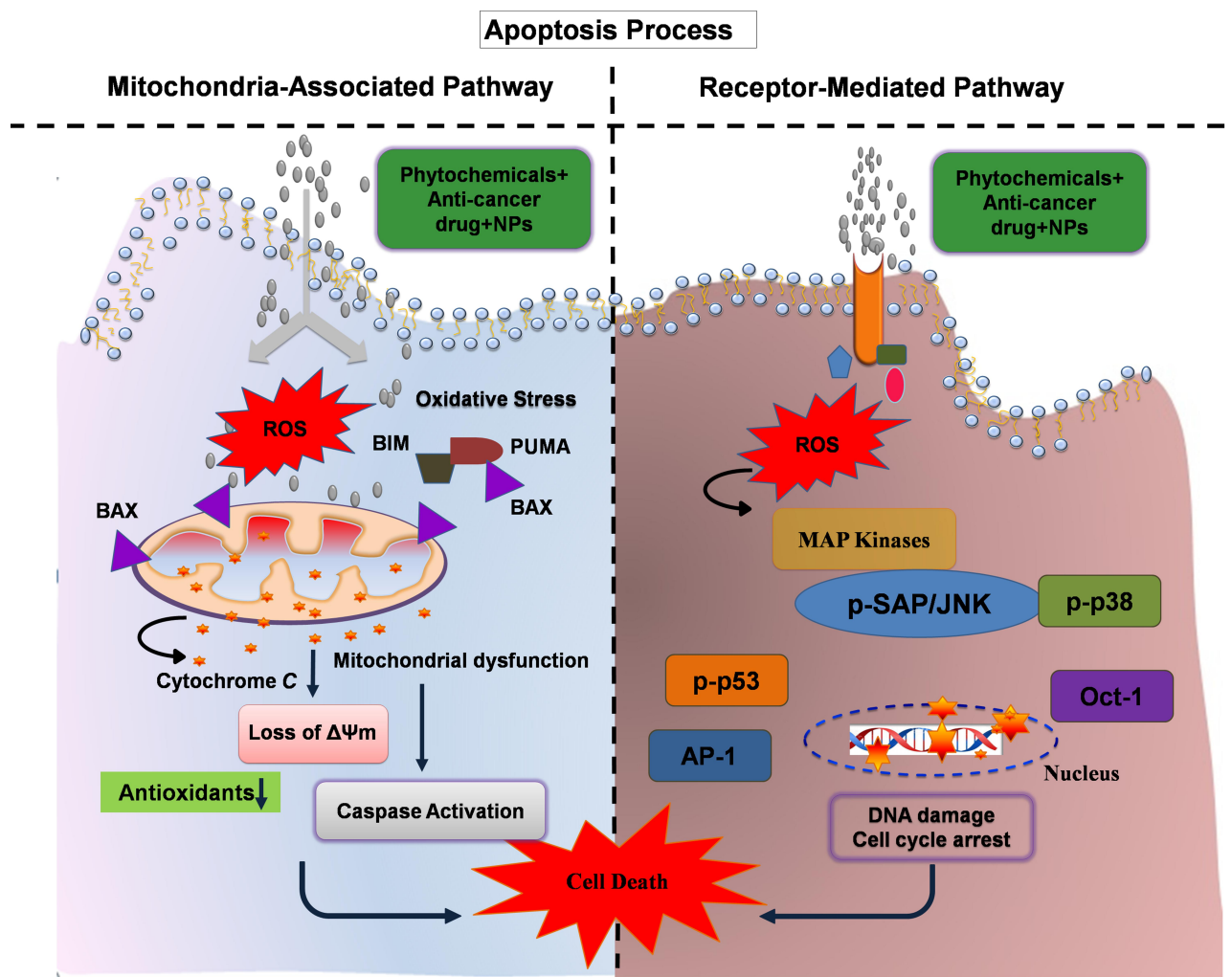


Figure 4 Intrinsic and extrinsic apoptotic cancer cell death mechanism with the treatment of phyto-nanocomposite inducing DNA damage and cell cycle arrest. Phytochemicals in combination with nanoparticles and anticancer drugs produce excessive ROS inducing oxidative stress that results in cancer cell death triggering various signaling pathways via mitochondrial and receptor-mediated apoptosis.

topoisomerase-I/DNA cleavage complex, further damaging DNA strand, disrupts cell cycle, and forcing cancer cells to undergo apoptotic death.¹⁶ Topotecan is either given alone or in combination for the treatment of ovarian and small-cell lung cancers and central nervous system tumors [NCT00611468, NCT00382733, and NCT01492673].

Belotecan Hydrochloride

Belotecan hydrochloride is a camptothecin analog with potential antineoplastic activity. Belotecan disrupts DNA replication, and induce cell cycle arrest compelling the tumor cells to undergo an apoptotic process of cell death. A multi-center (including 14 centers) randomized, open-label Phase III clinical trial was conducted to compare the treatment outcome of belotecan/cisplatin (BP) with the

conventional therapy of etoposide/cisplatin (EP) in naïve extensive-stage small cell lung carcinoma (ES-SCLC) patients. About 157 number of patients grouping into BP (n = 71) and EP (n = 76) were recruited for the trial. Results show BP arm had CR in one patient, partial response (PR) in 41, with stable disease (SD) response rate in 17 patients. However, non-inferior OS and PFS were found in both the EP and BP treatment arms. BP treatment regimen had raised concerns of grade 3 and 4 anemia along with thrombocytopenia, which suggests careful use of BP arm in further clinical trials.¹⁷ This drug is currently on clinical trials for the treatment of cervical cancers, small cell lung cancer, lung cancers, and ovarian cancer [NCT00430144, NCT01497873, and NCT01630018].

Irinotecan HCl [Topotecin]

Irinotecan hydrochloride (Topotecin) is a quinoline-based alkaloid and hydrochloride salt analog of natural product camptothecin. This drug forms active SN 38 (7-ethyl-10-hydroxy-camptothecin) metabolite which is 1000 fold more effective in inducing cell cycle arrest at S-G2 phase and apoptosis compared to the parent drug. This drug appears to stabilize reversibly topoisomerase complex acting as topoisomerase inhibitor, halting DNA ligation by breaking DNA single-strand resulting in irreversible blockage of DNA synthesis, causing cancer cell death. CAMPTOSAR® (Irinotecan HCL) injection is approved by the US FDA, in 2004, for the therapeutic application of metastatic colorectal cancer (CRC) as a combinatorial intravenous therapy with 5-fluorouracil (5-FU)/leucovorin.¹⁸ After several phase III clinical studies, the most frequent dosing of irinotecan treatment is an intravenous infusion of 300–350mg/m² for 30–90mn weekly for 6 weeks of the treatment cycle. Surprisingly, irinotecan has increased the OS (over 30months) of metastatic CRC patients dramatically, acting as a key anticancer regimen in combinatorial therapy with 5-FU. However, irinotecan-related drug toxicity can be overcome by lowering dose concentration in older and organ dysfunction cancer patients.¹⁸ This prodrug is used in combination or alone for the treatment of colorectal cancers, small cell lung cancer, and gastric cancer patients [NCT01114555, NCT01220063, and NCT00003748].

Gimatecan [STI481]

Gimatecan is a lipophilic semisynthetic derivative of camptothecin, with potential antitumor activities. Gimatecan, an orally active topoisomerase-I inhibitor, apoptotic inducer, currently under clinical trials for the treatment of brain and central nervous system tumors, advanced solid tumors, advanced epithelial ovarian, peritoneal and fallopian tube cancer [NCT00410358, NCT00032903, and NCT04029909].

9-Amino-20(S)-Camptothecin [9-Amino-CPT]

9-Aminocamptothecin is a camptothecin derivative of water-soluble pyranoindolizinoquinoline, with antineoplastic activities. The 9-amino-CPT drug is under clinical trials for the treatment of gastric cancer, ovarian cancer, lung, and kidney cancer [NCT00002635, NCT00003551, and NCT00002671] as an inhibitor of cell cycle and inducer of apoptosis.

10-Hydroxy Camptothecin [AR67]

AR-67 (7-t-butylidimethylsilyl-10-hydroxycamptothecin) is a pyranoindolizinoquinoline of natural plant-based camptothecin analog, which is highly potent, lipophilic and prolonged stable in blood. AR67 is a potent anticancer drug inducing DNA damage and apoptosis and is well tolerated by cancer patients. A Phase I clinical study using third-generation novel lactone form AR-67 with a dose of 1.2–12.4mg/m², daily infused for 1hr for 5days, every 21 days cycle, conducted in refractory solid tumor patients. The results show that AR67 drug was well tolerated without any infusional allergic reactions and diarrhea and highly stable (87% of the total drug-infused) in blood as active lactone form. Partial response (PR) was noted for a longer period in non-small cell lung cancer (NSCLC) patient and stable disease (SD) was observed in NSCLC, small cell lung cancer (SCLC), and duodenal cancer. However, accepted toxicity of febrile neutropenia, exhaustion, thrombocytopenia were observed, which were limited with reduced dose concentration to 7.5 mg/m² for every cycle of the treatment protocol.²⁰ Several clinical trials were ongoing in glioblastoma multiforme and metastatic solid malignancy patients to further warrant therapeutic efficacy of AR67 [NCT00956787, NCT01202370, and NCT00389480].

Karenitecin [Cositecan]

Karenitecin is a lipophilic, silicon-containing camptothecin derivative, with antineoplastic activities. It is under clinical trials for the treatment of ovarian cancer, brain tumors, non-small cell lung cancer, because of its higher stability, higher bio-availability, and enhanced tumor tissue penetration ability compared to the parent drug [NCT00010218, NCT00062478, and NCT00477282]. It blocks the cell cycle and induces apoptosis in cancer tissues.

Exatecan Mesylate Anhydrous [Mesylate]

Exatecan Mesylate is a water-soluble camptothecin derivative, with potent antitumor activity. Mesylate is a topoisomerase-I inhibitor, damages DNA triggering apoptosis in cancer cells. This agent is under clinical trials for the treatment of pancreatic cancer, refractory rhabdomyosarcoma, non-small cell lung cancer [NCT00045318, NCT00055939, and NCT00005091].

Elomotecan [BN80927]

Elomotecan is a camptothecin analog of having a stable β -hydroxy lactone ring, with antineoplastic activities.

Elomotecan is under clinical trial, a very potent antiproliferative agent used to treat cancer specifically malignant solid tumors [NCT01435096].

Namitecan [ST-1968]

Namitecan is a camptothecin analog, which has been used in clinical trials studying the treatment of Solid Tumors [NCT01748019]. This anticancer drug has S-phase specificity to inhibit cell cycle and induce apoptosis.

DRF-1042 [5-(2'-Hydroxyethoxy)-20(S)-Camptothecin]

DRF-1042 is a derivative of camptothecin, with anti-neoplastic properties. This drug has cell cycle inhibition and apoptotic activities. A phase I clinical trial on the dose-escalation experiment of DRF-1042 was conducted in refractory solid tumor patients. DRF-1042 was administered at a dose concentration of 1.5 to 270 mg/m², daily for 5day, every 2 weeks for 21 days. Results show 2CR, 2PR, and 4SD, but with delayed toxicity of grade 4 diarrhea and myelosuppression. The half-life of the drug found to be 9.9h-29h. The recommended dose of phase II trial is 80 mg/m² daily as per the treatment protocol. DRF-1042 is used in a phase-I trial for the treatment of prostate, colon, lung, and kidney tumors and has shown effective anticancer effect undergoing phase-II trials.²¹

Vincristine Sulfate [Kyocristine]

Vincristine Sulfate is a natural alkaloid extracted from the plant *Vinca rosea* Linn. (Apocynaceae) with potent anti-neoplastic efficacy. Vincristine has antimitotic properties, depolymerizes microtubules further arresting tumor cells in S-phase and M-phase of the cell cycle. This drug is used as a major chemotherapy regimen, that works in versatile ways to control the growth of cancer cells, either by apoptotic cell death or by cell cycle phase arrest, stopping the cell division process. Vincristine is approved by the US FDA, in 1963, as Oncovin, for the treatment of leukemias such as lymphoblastic lymphoma, Burkitt lymphoma, Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) and also solid tumors for all the group.²² A large spectrum of clinical trials continuing for further improvement of this drug efficacy [NCT00495079, NCT00022555, and NCT00516295].

Vinorelbine Tartrate

Vinorelbine tartrate is a bitartrate salt of alkaloid isolated from the *Vinca rosea* L. (Apocynaceae) leaves, with anti-tumor activities. Vinorelbine has antimitotic properties by inhibiting microtubule polymerization and results in apoptosis. A Phase II clinical study using vinorelbine as a single chemotherapy agent (25mg/m², weekly for 8 weeks) in metastatic gastroesophageal adenocarcinoma patients show a median OS of 7.8 months but with mild toxicity including myelosuppression, neutropenia, and constipation. Vinorelbine tartrate is approved by US FDA, as brand name Navelbine, in 1994, for the treatment of non-small cell lung cancer, advanced gastroesophageal adenocarcinoma, and breast cancer.^{23,24} Thousands of clinical trials ongoing using the vinorelbine as a major chemotherapy agent in patients with various cancer types such as metastatic breast, esophageal squamous cell carcinoma, and lung cancer [NCT00432562, NCT00675597, and NCT01222715].

Vinflunine Ditartrate [Javlor]

Vinflunine ditartrate is a novel bi-fluorinated derivative of alkaloid vinorelbine extracted from the plant *Vinca rosea* L. (Apocynaceae), with antitumor activities. Javlor has anti-angiogenic, antimicrotubule, and antimitotic activities inducing mitotic cell cycle arrest at the G2/M phase, resulting in apoptotic cancer cell death. Vinflunine ditartrate infused as monotherapy in adult advanced transitional cell carcinoma of the urothelial tract (TCCU) as second-line therapy after failure of the first-line platinum-based regimen. In a multi-center, phase III clinical experiment, 370 patients were randomly allotted the treatment with [vinflunine (VFL) + BSC (best supportive care), n-253], and BSC (n-117). The median OS rate of (VFL + BSC) treatment was 6.9 months, compared to 4.6 months of (BSC) arm. Although nonsignificant OS, PFS (progression-free survival) rate has a significant difference (3m of VFL compared to 1.5 m in BSC). This trial recommended a dose of 280–320 mg/m², 20mn infusion, every 21 days for the subsequent cycles.²⁵ Vinflunine was approved by the European Medicines Agency (EMA), in 2009, for the treatment of metastatic and advanced urothelial cancer where platinum-based treatment fails.²⁶ Currently, this drug has ongoing clinical trials for the treatment of various cancer types such as hormone-refractory prostate cancer (phase II), relapsed extensive SCLC (phase II), recurrent or metastatic head and neck carcinoma (phase III) [NCT00545766, NCT00284154, and NCT02347332].

Fosbretabulin Tromethamine [CA4P]

Fosbretabulin tromethamine, also known as combretastatin A4 phosphate (CA4P) is a water-soluble disodium salt of a natural phenol derivative, extracted from the plant *Combretum cafferum* (African bush willow), with potential antitumor properties. This is an antimicrotubule, antiangiogenic, and antimitotic agent. It depolymerizes microtubule assembly, disrupts mitosis, disrupts tumor vasculature, and facilitates apoptosis in the tumor cells. A Phase II clinical trial of CA4P in advanced nonsquamous NSCLC patients was conducted with dosing of 60mg/m² weekly for every cycle of 21 days. Results show CA4P treated patients have a 50% overall tumor response rate compared to 32% of the control group.²⁷ CA4P is ongoing with several clinical trials for the treatment of ovarian, epithelial, fallopian tube, neuroendocrine tumor, and lung cancer [NCT01305213, NCT02132468, and NCT00653939].

Ombrabulin [AVE8062]

Ombrabulin is a natural phenol derivative of combretastatin A4, extracted from the plant *Combretum cafferum* (Combretaceae), with potential antitumor properties. Ombrabulin binds to the colchicines binding site, inhibiting tubulin polymerization and inducing mitotic arrest and apoptosis in endothelial cells. In a phase I trial, antineoplastic agent ombrabulin (15.5–35 mg/m² infusion up to 30mn, the first day of every week for 3 weeks) has shown 1 CR, 15 PR in advanced solid tumor patients with feasibility up to 3 weeks regimen along with docetaxel.²⁸ Ombrabulin has been used in trials studying the treatment of sarcoma, neoplasms, solid tumors, malignant and advanced solid tumors, among others [NCT00699517, NCT01907685, and NCT01263886].

Idronoxil [Phenoxodiol]

Idronoxil, also known as phenoxodiol, flavonoid derivative of plant *Glycin max* Linn. (Fabaceae), with potent antineoplastic activities. This drug activates tumor cell apoptosis via activating caspase cascade and disrupting apoptosis inhibitors (XIAP). Idronoxil also induces cell cycle arrest by inhibiting DNA topoisomerase II and preventing the replication of DNA.²⁹ In a phase I trial, each metastatic solid tumor patient received phenoxodiol at 5 mg/kg over 5mn for 6 weeks of bolus infusion followed by 2 mg/kg/hr continuous infusion. This resulted in short half-life (0.67 ± 0.53 h and 3.19 ± 1.93 h) and fast rate of plasma clearance (2.48 ± 2.33

L/h and 0.15 ± 0.08 L/h,) even with continuous infusion of the drug, leading to rapid steady-state.³⁰ Phase I and phase III clinical studies on phenoxodiol as an anticancer drug for solid tumor, prostate cancer, and ovarian cancer treatment suggested that phenoxodiol as a broad spectrum chemo-sensitizer, tumor-specific and multi-pathway apoptosis-inducing drug.^{30,31} This drug has several ongoing clinical trials on patients having fallopian tube cancer and prostate cancer [NCT00382811, NCT00557037, and NCT00382811].

Genistein

Genistein is a phytoestrogen isoflavone, isolated from the plant *Glycin max* Linn. (Fabaceae), with antineoplastic, antioxidant properties. Mechanistic intuition of Genistein depicts its potential for inhibition of topoisomerase-II and protein-tyrosine kinase activity, leading to cell cycle arrest at the G2/M phase and apoptosis induction, as well as antioxidant, antiangiogenic, and anti-inflammatory properties.^{10,32} Genistein has been used for the treatment of metastatic colorectal cancer (phase I/II), early-stage prostate cancer (phase II), stage IV breast cancer (phase II) under various clinical trials [NCT01985763, NCT01325311, and NCT00244933].

Ingenol Mebutate [PEP 005]

Ingenol mebutate [PEP 005] is a salt of ingenol, extracted from the plant sap of *Euphorbia peplus* (Euphorbiaceae), with potent antineoplastic activities. This agent is a protein kinase C (PKC) activator, regulated cell cycle inducing apoptosis in various cancer certain tumor cells, including myeloid leukemia cells, melanoma cells, and basal cell carcinoma cells. Recently, the US FDA approved this drug, in 2012, for the actinic keratosis topical treatment.³³ This drug is under various cancer treatment trials of basal cell carcinoma (phase I/II) and non-invasive lentigo melanoma of the face (phase II) [NCT03569345, NCT00108121, and NCT02723721].

Betulinic Acid

Betulinic acid is a lupane of pentacyclic triterpenoid betulin, extracted from the bark of the plant *Betula pubescens* (Betulaceae) with anti-inflammatory and antineoplastic activities. It is a DNA topoisomerase inhibitor, induces apoptosis via mitochondrial disruption, activating caspase cascades.³⁰ A phase-I trial is ongoing as a topical ointment for the treatment of cutaneous metastatic melanoma [NCT00701987].

Maytansine

Maytansine is a macrocyclic lactam antibiotic extracted from the bark of shrub *Maytenus ovatus* (Celastraceae) with potent antineoplastic activities. It is an anti-tubulin, antimetabolic drug used in combination with an antibody (ADC) called Trastuzumab emtansine. The only maytansinoid-based ADC, approved by the US FDA, in 2013 is trastuzumab for the treatment of HER2-positive metastatic breast cancer.³⁵ This drug is under trials to treat various cancer types such as metastatic non-small cell lung cancer (NSCLC) (phase II), advanced breast cancer (phase I/II), and colorectal cancer [NCT02289833, NCT00934856, and NCT01641939].

Sulforaphane

Sulforaphane is a natural isothiocyanate isolated from crucifer plant *Brassica oleracea* (Brassicaceae), with potent anticancer effects. It is a secondary plant metabolite having antioxidant, antimetabolic, and antiangiogenic properties. It acts through (i) blocking mutagen action; (ii) inhibiting cell cycle and inducing apoptosis clearing tumor cells; (iii) disrupting neoangiogenesis in cancer metastasis.³⁶ Currently, this drug is under various clinical trials for the treatment of cancer such as lung cancer (phase II), prostate cancer (phase II), metastatic breast cancer (phase II) [NCT03232138, NCT01228084, and NCT02970682].

Epigallocatechin Gallate [EGCG]

Epigallocatechin gallate is a polyphenol, flavan and gallate ester, catechin, isolated from the tea plant *Camellia sinensis* (Theaceae). It acts as an antioxidant, anti-Hsp90, anti-neoplastic agent, with neuroprotective activities.³⁷ This drug is under the clinical trial of various cancer treatments including colorectal cancer (phase I), lung cancer (phase II), and prostate cancer undergoing surgery (phase I) [NCT02891538, NCT02577393, and NCT00459407].

Curcumin

Curcumin is a polyphenol (beta-diketone), a purified extract of turmeric root obtained from ferulic acid and originally isolated from the Indian plant *Curcuma longa* (Zingiberaceae). It has antifungal, antibacterial, and antineoplastic activities. It has been approved by the US FDA (GRN-686) as “Generally Recognized As Safe” (GRAS).³⁴ This drug is under clinical trials for the treatment of several cancer types such as breast cancer, pancreatic, and prostate cancer [NCT01917890, NCT01160302, and NCT02554344].

R-(-)-Gossypol Acetic Acid

R-(-)-Gossypol acetic acid is a polyphenol (gossypol) isolated from the seeds of the plant *Gossypium herbaceum* (Malvaceae), also a BCL-2 homolog domain 3 mimetic, comprising of R-(-) enantiomer solvate of the gossypol along with acetic acid with potential antitumor activity. R-(-)-Gossypol acetic acid intercalates with antiapoptotic proteins (Bcl-2 and Bcl-xL) for separating proapoptotic proteins (Bid, Bad, and Bim) to enhance apoptosis process through cell cycle arrest at G0/G1 phase, hence restricting tumor cell proliferation.³⁹ This drug has tremendous scope to qualify as an anticancer drug and currently under phase I/II clinical trials for the treatment of 78 more cancer types including multiple myeloma, lung cancer, prostate cancer, and solid tumor [NCT00773955, NCT00397293, and NCT00666666].

Beta-Lapachone [ARQ 501]

β -Lapachone is a natural ortho-naphthoquinone and a bark extract from the tree *Tabebuia avellanedae* (Bignoniaceae), with antineoplastic properties. Beta-lapachone generates high levels of ROS (reactive oxygen species) that induce DNA damage, resulting in cell cycle arrest and apoptosis, upon activation with NQO1 (quinone oxidoreductase-, a flavoprotein). Hence, this drug can be effective in treating tumors overexpressing NQO1.⁴⁰ β -Lapachone is under various clinical trials for the treatment of carcinoma, pancreatic cancer, solid tumors, head and neck neoplasm, lymphoma, and carcinoma [NCT00524524, NCT00099190, and NCT00358930].

Cryptophycins 52 [LY355703]

Cryptophycins 52, is a cytotoxin, initially isolated from blue algae called cyanobacteria (Nostoc sp. ATCC 53,789, Nostoc sp. GSV 224) of Nostocaceae family, a potent microtubule inhibitor, with potential antineoplastic properties. Upon treatment it disrupts microtubule, preventing cell cycle and results in apoptosis. Cryptophycins 52, has completed phase-II clinical trials for the treatment of platinum-resistant ovarian cancer and advanced non-small cell lung cancer.^{41,42} In a phase II trial, Cryptophycins 52 chemo-drug administered at 1.125–1.5 mg/m² on days 1 and 8 for every 3 weeks, assessed for every 2 cycles in advanced non-small cell lung cancer patients. Results show reduced toxicity but unacceptable levels of peripheral neuropathy toxicity observed at 1.5 mg/m² dose concentration. SD rate of 40% was evident. This mandate substantial change in dosage protocol for further clinical trials.⁴²

Lovastatin

Lovastatin is a natural statin, a delta lactone, a polyketide, a fatty acid ester, a HMG-CoA reductase inhibitor, isolated from oyster mushroom *Pleurotus ostreatus* (Pleurotaceae) with antitumor properties. This drug is under clinical trial for the treatment of melanoma, breast cancer [NCT00462280, NCT00584012, and NCT00902668].

Kanglaite [Coix Seed Oil]

Kanglaite is a form of natural oil extracted from the seeds of plant *Coix lacryma-jobi* (Cramineae) with antineoplastic activity. The therapeutic formulation is an injectable microemulsion of purified coix seed oil. Although the drug mechanism of action is unclear, kanglaite significantly reduces tumor via cell cycle arrest at the G2/M phase, eventually resulting in apoptosis of cancer cells. This drug has been approved in China (1995) for hepatocellular carcinoma and advanced non-small cell lung cancer treatment.⁴³ Over 20 years of observation taking millions of patients from multiple countries has shown effective outcomes without side effects. Currently, this drug is under the US FDA approval process.⁴³ Kanglaite is under clinical trials for the treatment of pancreatic cancer, non-small cell lung, and cachexia [NCT02553187, NCT03986528, and NCT00733850].

Simvastatin

Simvastatin is a hydroxymethylglutaryl-CoA reductase inhibitor, extracted from the fungus *Aspergillus terreus* (Trichocomaceae), with antineoplastic activities. It lowers tumor proliferation by restricting its growth at the G0/G1 phase of the cell cycle, inducing apoptotic cancer cell death. In a phase-II clinical trial, simvastatin is found to reduce recurrence of the breast cancer through modulation of estrone sulfate concentrations by reducing its chemoresistance activity.⁴⁴ Breast cancer patients of stage 0-III administered with oral simvastatin (40 mg) for 24–28 weeks. Results show a significant reduction in lipid profile and cancer marker high-sensitivity C-reactive protein (hsCRP) by limiting estrone sulfate concentrations. This clinical study suggests the feasibility of Simvastatin in chemoresistant breast cancer treatment. Simvastatin drug is currently used in combination with other drugs undergoing clinical trials for the treatment of metastatic breast cancer, adenocarcinoma of the rectum, stomach cancer, pancreatic cancer, and prostate carcinoma [NCT03324425, NCT00334542, and NCT00944463].

Paclitaxel [Taxol]

Paclitaxel, a microtubule inhibitor with a tetracyclic diterpenoid structure, extracted from the tree *Taxus brevifolia* (Taxaceae) bark, is currently being used for the therapy of breast, ovarian, pancreatic, and lung cancer. Paclitaxel arrest cells growth and division by blocking the cell cycle G2/M phase inducing apoptosis in cancer cells. Armstrong et al demonstrated that paclitaxel when administered intravenously with intraperitoneal cisplatin significantly improved overall survival rate and progression-free survival in patients with stage-III ovarian cancer.⁴⁵ Paclitaxel, although associated with mild asymptomatic liver transaminase elevation, however, clinical liver failure has not been documented. It received FDA approval for the treatment of refractory breast cancer back in 1992.

Taxoprexin [DHA-Paclitaxel]

DHA-Paclitaxel is a combination of a natural fatty acid (DHA) and paclitaxel, with antineoplastic activities. It is a type of mitotic inhibitor, has been studied as first-line treatment in patients with stage IIIB/IV non-small-cell lung cancer. As a single-agent, the combination has little activity in patients with advanced non-small-cell lung cancer, with less than half of patients achieving either disease stability or responding partially. However, the survival advantage achieved is comparable with the more toxic standard platinum-based combination chemotherapy. Myelosuppression is a major dose-related toxicity of Taxoprexin.⁴⁶ DHA-Paclitaxel is currently ongoing clinical trials for the treatment of non-small cell lung cancer, metastatic melanoma [NCT00244816, NCT00249262, and NCT00243867].

Larotaxel [XRP9881]

Larotaxel, a semi-synthetic taxane, with good blood-brain barrier (BBB) permeability. It prevents microtubule depolymerization by binding to and stabilizing microtubule assembly, leading to cell cycle arrest at the G2/M phase and apoptosis. Due to less affinity for P-glycoprotein, this agent may be useful for treating multi-drug resistant tumors. In advanced/metastatic NSCLC patients, larotaxel in combination with carboplatin has shown promising efficacy and lower neutropenia toxicity.⁴⁷ Larotaxel has been used in clinical trials for the treatment of breast neoplasms and pancreatic adenocarcinoma, among others [NCT00387907, NCT00417209, and NCT00625664].

Ortataxel [IDN-5109/BAY 59-8862]

Ortataxel is a second-generation derivative of taxane, isolated from tree *Taxus baccata* L. (Taxaceae) with potential antitumor activity. It inhibits cell proliferation by binding to microtubule arresting cell cycle phase arrest. Structurally, a semi-synthetic taxane and functionally, a microtubule stabilizer, it interacts and interferes with the microtubule assembly/disassembly, thereby leading to arrest of cell cycle and tumor proliferation. Exhibiting poor affinity for P-glycoprotein, multidrug resistance protein (MRP-1) and breast cancer resistance protein (BCRP) mediated efflux, it holds the potential for the treatment of multidrug resistance (MDR) tumors expressing these proteins.⁴⁸ Ortataxel has been studied in clinical trials for the treatment of glioblastoma, lymphoma, and neoplasia of the kidney and lungs [NCT01989884, NCT00054314, and NCT00039169].

MAC 321 [Milataxel]

Milataxel, orally bioavailable taxane, acting as a microtubule stabilizer in conjunction with its active metabolite M-10, it inhibits the depolymerization of microtubules and arrests the cell cycle in the G2/M phase, leading to its antiproliferative effect on neoplastic cells. Due to less affinity for multidrug-resistant (MDR) membrane-associated P-glycoprotein, this agent may be useful for treating MDR tumors. A phase II study of milataxel in previously treated patients with advanced colorectal cancer did not show any favorable clinical outcome. However, a clear risk of line threatening neutropenic sepsis and diarrhea were noted in the subjects receiving the molecule, demanding closer surveillance.⁴⁹ Milataxel is under clinical trials for the treatment of mesothelioma, lung cancer, and colorectal cancer [NCT00685204, NCT00063219, and NCT00063427].

UNII-A2VM2V569A [TPI-287]

TPI 287, a structurally modified synthetic taxane with better central nervous system (CNS) penetration and with the ability to evade potential multidrug resistance efflux pump mechanisms, with antineoplastic activities. The drug is currently undergoing a phase-1 trial for the treatment of metastatic melanoma, which aims to establish the maximum tolerable dose of the combination.⁵⁰ Another Phase-1 study of 18 patients with refractory/recurrent neuroblastoma or medulloblastoma in combination with temozolomide showed good toleration among the pediatric

population at a dose of 125 mg/m² on days 1, 8, and 15 of a 28-day cycle.⁵¹

BMS-275,183 [Oral Taxane]

BMS-275,183 is an oral taxane, with antineoplastic activities. It has been used in trials studying the treatment of non-small cell lung cancer (NSCLC). A Phase I–II dose-ranging study of BMS-275,183 in combination with pemetrexed (Alimta) in patients with recurrent NSCLC is underway. The trial aims to study the safety and efficacy of this combination treatment [NCT00103831].

DJ 927 [Tasetaxel]

DJ 927 is a semi-synthetic oral taxane with antimetabolic, anti-VEGF, and antineoplastic properties. It prevents microtubule depolymerization by binding to and stabilizing microtubule assembly, leading to cell cycle arrest and tumor cell proliferation. Due to less affinity for P-glycoprotein, this agent may be useful for treating multi-drug resistant tumors.⁵² Tasetaxel has been used in trials for the treatment of gastric carcinoma, metastatic melanoma, prostate cancer, and advanced solid tumors, among others [NCT01064713, NCT00077077, and NCT01573468].

Cabazitaxel [Jevtana]

Cabazitaxel, a Microtubule inhibitor and a semi-synthetically derived molecule from natural taxoid 10-deacetylbaccatin III, is currently used for castration-resistant metastatic prostate cancer which has failed treatment with docetaxel.⁵³ It prevents microtubule depolymerization by binding to and stabilizing microtubule assembly, leading to cell cycle arrest and tumor cell proliferation. In 2009, the US FDA approved Jevtana for prostate cancer treatment only in combination with prednisone to be administered intravenously.⁵³ Due to less affinity for P-glycoprotein, this agent may be useful for treating multi-drug resistant tumors. Currently, this drug is under clinical phase trials for the treatment of malignant solid tumor, malignant nervous system neoplasm, NSCLC, metastatic prostate cancer [NCT01751308, NCT01438307, and NCT01308580].

Elliptinium Acetate [Celiptium]

Celiptium is an alkaloid derivative of ellipticine, isolated from plant *Bleekeria vitensis* (Apocynaceae), its acetate salt has anti-neoplastic properties. A topoisomerase II inhibitor and intercalating agent, it induces DNA breakages, thereby inhibiting transcription and translation of proteins. It is presently undergoing Phase II study for

salvage treatment (weekly dosage) of advanced breast cancer. The 3-week schedule found to be less toxic compared to the weekly regimen.⁵⁴

Omacetaxine Mepesuccinate [Synribo]

Omacetaxine is a semisynthetic cephalotaxine alkaloid ester isolated from the plant *Cephalotaxus harringtonia* var. *drupacea* (Cephalotaxaceae) leaves; that acts as a protein translation inhibitor and is used to treated chronic myeloid leukemia that is resistant to tyrosine kinase receptor antagonists. Most recently, this drug is approved by the US FDA, in 2012, for patients of tyrosine kinase inhibitors resistant accelerated/chronic phase CM.⁵⁵ Subcutaneous omacetaxine mepesuccinate accelerates tumor cell death leading to tumor cell clearance. Omacetaxine Mepesuccinate is currently under clinical trial to treat various cancer types such as leukemia and solid tumors [NCT00006364, NCT00462943, and NCT00675350].

Nanotechnology in Cancer Diagnosis and Target-Specific Treatment as Phyto-Nanoformulations

Nanomedicine invention and development have exceedingly advanced during the past few years. Nanoparticles conjugated plant extract-anticancer drugs have significantly superior potency compared to its conventional therapy as it can cross bio-membrane barriers spontaneously owing to its nanosize and surface reactivity to achieve required concentrations in tumor with slower elimination, without harming surrounding normal tissues from drug toxicity. Nanodrug constructs also facilitate the enhanced localization of tumors as contrast agents as well as efficient delivery of different anticancer therapeutics under control of external (UV-rays, X-ray, laser ray) or internal (pH, temperature, redox) stimuli for surgically impervious malignant tumors.^{56–59} Numerous plant-based anticancer nanoformulations have been approved by the FDA, and dozens are in clinical trials. Most recently approved nanomedicine core materials are based on previously approved conventional drugs.

Active and passive targeting using nanodrugs via inducing cell cycle arrest and apoptosis can provide a unique non-invasive approach to counter malignant tumors minimizing systemic toxicity.³ Active targeting is a superior and more precise way of cancer-targeting usually relies on the receptor-ligand reciprocity, in which nanodrug acts as a ligand that binds to the definite receptors on the tumor cell

surface, activating various signaling cascade, progressing apoptotic cancer cell death as depicted in Figure 4. The use of nanocarriers such as liposomes, micelle, dendrimers, nanodispersions, polymeric nanoparticles, nanotubes, nanorods, and metallic/non-metallic nanoparticles has ineluctably impacted cancer pharmacology.⁵⁹ Phytomolecules conjugated anti-neoplastic drugs in nano-size diffuse through the cell membrane escaping immune defense mechanism is known as passive targeting as depicted in Figure 4. Phyto-nanocomposite circulates through the cytoplasm, diffuse into intracellular organelles inducing oxidative stress and loss of mitochondrial membrane potential, progressing apoptosis in cancer cells. As aforementioned in Figure 4, phyto-nanocomposite clears tumor through active and passive targeting inducing oxidative stress, activating various signaling pathways, caspase activation in a controlled and target-specific manner. ROS above the threshold level causes oxidative stress, trigger apoptotic signals through modulating multiple signaling pathways, including the MAPK/JNK (mitogen-activated protein kinase/c-Jun N-terminal kinase), P38/MAPK pathway, MAPK/ERK (extracellular-signal-regulated kinase), SAPK (stress-activated protein kinases)/JNK, TRAIL (Tumour necrosis factor (TNF)-related apoptosis-inducing ligand) mediated pathway, PI3K/AKT (phosphoinositide-3-kinase/protein kinase B), P53 mediated apoptotic pathways, Caspase mediated, NFκB (nuclear factor κB), signaling pathways.⁸ Nanoparticles-based anti-neoplastic agents having phytomolecules have revolutionized conventional cancer therapy greatly advancing clinical practice. The present section followed by detailed coverage of the approved formulations in clinical use along with an insight of various phyto-nanodrug vehicle nanomedicines under clinical trials to clinical use in cancer therapeutics mentioned in Table 3.

Paclitaxel Albumin-Stabilized Nanoparticle Formulation [Abraxane®]

Abraxane is a Cremophor toxin-free, nanoparticle composite stabilized with human serum albumin using natural taxane paclitaxel as a core drug. This nano-formulation permits the administration of increased doses (4–5 folds) of paclitaxel as toxic cremophor is absent, along with reduced infusion time, eliminating premedication.⁶⁰ This drug is used alone or in conjugation to treat pancreatic cancer, metastatic breast cancer, lung cancer, and bladder cancer like many other cancer types. The new nano-

Table 3 List of Phytochemical-Based Nanoformulations Approved by the US FDA Under Clinical Trials to Clinical Use in Cancer Theranostics[#]

Phytochemicals	Trade Name	Manufacturing Company	Nanoformulations	Size (nm)	Mode of administration	FDA approved	Cancer type	References (Govt. Clinical trials)
Paclitaxel	Abraxane [®]	Celgene Co., Ltd	Albumin-stabilized nanoparticle formulation	130nm	Intravenous (IV)	Yes	Breast cancer, Non-small cell lung cancer, Pancreatic cancer	[60–64] NCT02555696 NCT02151149 NCT00691054
Paclitaxel	Lipusu [®]	Nanjing Luye Sike Pharmaceutical Co., Ltd.	Paclitaxel liposome injection of cholesterol and lecithin	150nm	IV	Phase-I/II/III/IV	Breast cancer, Non-small cell lung cancer, Ovarian cancer	[65] NCT02142790 NCT02996214
Paclitaxel	Genexol-PM/IG-001/ Cynviloq	Samyang biopharma Co., Ltd.	Paclitaxel-loaded polymeric micelle	23.91 nm	IV	Phase- I/II/III/IV	Breast cancer, Gastric cancer, Non-small cell lung cancer, Ovarian cancer, Bladder cancer, Pancreatic cancer	[66,67] NCT00912639 KCT0003607 NCT03618758
Paclitaxel	NK105	Nippon Kayaku Co., Ltd.	Paclitaxel-incorporating micellar nanoparticle	85 nm	IV	Phase-III	Breast cancer, Solid tumors	[68] NCT01644890
Irinotecan	Onivyde [®]	Merrimack Pharmaceuticals Inc., Cambridge, USA	Irinotecan hydrochloride liposome	110nm	IV	Yes	Pancreatic cancer, Refractory pediatric malignancies, NSCLC, Advanced breast cancer	[69] NCT00702182 NCT01494506 ChiCTR-IPR-15005856
Vinorelbine tartrate	Navelbine/ [®] NanoVNB [®]	Pierre Fabre Pharmaceuticals, Inc.	Liposomal vinorelbine tartrate	94.8 ± 1.5nm	IV	Yes	Non-small cell lung cancer, Breast cancer, Ovarian cancer	[70] NCT03518606 NCT00153907 NCT00148668 NCT02925000

(Continued)

Table 3 (Continued).

Phytochemicals	Trade Name	Manufacturing Company	Nanoformulations	Size (nm)	Mode of administration	FDA approved	Cancer type	References (Govt. Clinical trials)
Vincristine	Marqibo®	Talon Therapeutics Co., Ltd	Vincristine sulfate liposome	163nm	IV	Yes (Phase I/III/III/IV)	Acute lymphoblastic leukemia (ALL)	[71] NCT00495079 NCT00145041 NCT00144963 NCT01026220
Camptothecin	L9-NC	M.D. Anderson Cancer Center	Liposomal 9-nitrocamptothecin	190nm	IV	Phase-I/II	Endometrial cancer, Ewing's sarcoma	[72] NCT00492141 NCT00249990
Camptothecin	CRLX101/NLG207	UNC Lineberger Comprehensive Cancer Center	Polymer nanoparticle formulation of camptothecin	< 100 nm	IV	Phase-I/II	Rectal cancer, Advanced non-small cell lung cancer, Metastatic Gastroesophageal cancer	[73-75] NCT02010567 NCT01380769 NCT01612546
Curcumin	Lipocurc™	SignPath Pharma Co., Ltd	Liposomal curcumin	170nm	IV	Phase-I/II	Solid tumors	[76,77] NCT02138955
Curcumin	IMX-110	Immix Biopharma Australia Pty Ltd	Curcumin/doxorubicin-encapsulating nanoparticle	30-400 nm	IV	YES (Phase I/II)	Advanced solid tumors	NCT03382340
Docetaxel	LE-DT/ATI-1123	NeoPharm, Inc	Liposomal docetaxel	100nm	IV	Phase-I/II	Solid tumors	[78,79] NCT01151384
Docetaxel	Docetaxel ^{PM} /SYP-0704A/NANOXEL-M	Samyang Biopharmaceuticals Co., Ltd	Docetaxel polymeric micelle	10-30nm	IV	Phase-II/III,	Head and neck squamous cell carcinoma, Bladder cancer, Esophageal Carcinoma	NCT02639858 NCT02982395 NCT01336582 NCT03585673
Docetaxel	CriPec® docetaxel/CPC634	Cristal Therapeutics	Docetaxel containing CriPec nanoparticles	66nm	IV	Phase-I/II	Solid tumors ovarian cancer	[80,81] NCT02442531 NCT03742713 NCT03712423

Docetaxel	SYP-0709	Samyang Biopharmaceuticals	Docetaxel- polymeric nanoparticles (DOC-PNP)	10~1000nm	IV	Phase-I	Advanced solid cancer	NCT02274610 NCT01103791
Docetaxel	CRLX301	Cerulean Pharma Inc.	Docetaxel-loaded nanopharmaceuticals	20~200nm	IV	Phase-III	Solid tumor	[82,83] NCT02380677
Docetaxel	DoceAqualip	Intas Pharmaceuticals Ltd	Nanosomal docetaxel lipid suspension (NDLS)	<100 nm	IV	Phase-I/II/III, Approved in India	Solid tumor; Prostate cancer; Breast cancer; Squamous cell carcinoma of the head and neck; Gastric adenocarcinoma	[84-86] NCT01957995 NCT03671044

Note: #Source: US National Library of Medicine.

formulation binds to the albumin receptor of the endothelial cells and the other proteins overexpressed in cancer cells to transfer drugs into the cytoplasm. Nano-size cancer drugs achieved higher intratumoral accumulation and better bioavailability compared to its conventional paclitaxel alone improving the cancer therapeutic index in various cancer types.⁶⁰

Breast Cancer Treatment

Breast cancer leads to be the topmost prevalent cancer in women among other cancer types worldwide. Among breast cancer drugs, paclitaxel found to be the most effective, in contrast to possessing severe toxic side effects. To overcome such strong toxic effects, nano-formulation like nab-paclitaxel has reached pivotal clinical trials and approved to be used for breast cancer treatment. Gradishar et al in 2005, administered intravenously nab-paclitaxel (260 mg/m²) with no premedication to 299 patients and with conventional paclitaxel (175 mg/m²) including premedication to other groups of 225 patients at the three-week schedule. The results demonstrated that nano-formulation has improved response over conventional one with lower neutropenia, low toxicity profile, and increased survival advantage.⁶⁰ Consistently, in 2012, an updated study has been published by Gradishar et al which demonstrated that nab-paclitaxel (150 mg/m²) impressively prolonged overall survival rate compared to nab-paclitaxel (100/300 mg/m²) and docetaxel (100 mg/m²) when administered to 302 patients with metastatic breast cancer. Altogether nab-paclitaxel reduced fatigue, and febrile neutropenia like severe side effects, proving it to be the most clinically efficacious anti-neoplastic drug for patients with metastatic breast cancer.^{60,61}

Pancreatic Cancer Treatment

Pancreatic cancer is one of the biggest fatal malignancies and aggressive, most prevalent in middle-aged men. It occupies the first place as asymptomatic cancers, predominantly pancreatic adenocarcinomas. Nano-formulation of Nab-paclitaxel and gemcitabine combinatorial drug becomes a standard first-line therapy in metastatic pancreatic adenocarcinomas. A case study by Von Hoff et al in 2013, suggested that in a phase-III trial, nab-paclitaxel plus gemcitabine significantly increased the overall survival rate of metastatic pancreatic adenocarcinomas patient (n=431) with improved safety and lesser side effects after getting a substantial positive response of nab-paclitaxel in phase-I/II clinical trial.⁶² Also, Petrillo et al demonstrated

that nab-paclitaxel plus gemcitabine is a good choice for geriatric populations as daily clinical practice in metastatic pancreatic adenocarcinoma treatment.⁶³

Lung Cancer Treatment

Lung cancer such as non-small cell lung cancer (NSCLC) is the topmost prevalent cancer type among men. NSCLC is with high risk for clinical chemotherapy regime trials because of its recurrence. A report by Asahina et al in 2019, demonstrated that in a phase-III trial, the overall response rate (ORR) reached to 66.7% to meet the primary endpoint, median progression-free survival (PFS) increased to 8.2 months, and overall survival (OS) improved to 16.8 months with acceptable toxic effects, when NSCLC patients treated with 100 mg/m² nab-paclitaxel weekly and carboplatin once every 3 weeks continued for 3–4 cycles.⁶⁴

Paclitaxel Liposome [Lipusu®]

Liposome-encapsulated nano-formulation of paclitaxel developed in 2003, which exhibits higher potency of increased solubility, lower cytotoxicity, slow elimination, high tissue concentration, and better pharmacokinetics as compared to paclitaxel alone. Liposomal paclitaxel is cremophor EL free which has severe toxic effects like anaphylaxis. A report by Xu et al demonstrated that liposomal paclitaxel has a better performance compared to paclitaxel alone when infused the same dose of 135 mg/m² up to 4 cycles (for >3 h on the first day of each cycle comprising of 21 days) in patients with metastatic gastric cancer. Cremophor EL free Lipusu and paclitaxel alone have nearly the same response rate (47% and 46%) but liposomal formulation has significantly lower toxic effects like vomiting, nausea and hypersensitivity reactions, as it does not need pre-medications of antihistamines like the conventional one.⁶⁵

Paclitaxel-Loaded Polymeric Micelle [Genexol-PM®]

Paclitaxel-loaded polymeric micelle is an mPEG (methoxy polyethylene glycol)-PDLLA (D/L polylactic acid) solubilizer based nanoparticle-polymeric micellar formulation of paclitaxel (Genexol PM) with antineoplastic properties. Paclitaxel binds with polyethylene glycol (PEG) covalently forming a micellar structure having outer PEG shells (hydrophilic) encapsulating the paclitaxel (hydrophobic). This nanodrug is cancer tissue targeted, pH-responsive, and stays stable for a long time in the bloodstream. Upon low pH stimuli in tumor tissue this

drug is released slowly into the tumor microenvironment, accumulates in higher doses with less toxicity to the normal cells. This nano-micellar formulation has improved pharmacokinetics, high solubility, reduced hypersensitivity, superior efficacy, and low toxicity. A report by Lee et al in 2018 demonstrated that micellar Genexol-PM (260mg/m²) with carboplatin every 3 weeks for 6 cycles has given to the epithelial ovarian cancer patients in a phase-II trial, shown ORR of 88.0% with manageable toxicity of neutropenia and peripheral neuropathy.⁶⁶ In 2017, Park et al group has reported that Genexol-PM (246.8±21.3 mg/m²), over 24.5 months of median follow-up show better ORR of 39.1% and improved toxicity toleration in a phase-III trial of 212 metastatic breast cancer patients in comparison to standard paclitaxel (Genexol) when given intravenously for every 3 weeks.⁶⁷

Paclitaxel-Incorporating Micellar Nanoparticles [NK105]

A Paclitaxel-incorporating micellar nanoparticle (NK105) is a novel radiosensitizing PEG-polyaspartate micellar nanoparticle formulation encapsulating paclitaxel with antineoplastic effect. Recently in 2019, a report by Fujiwara et al demonstrated in a phase-III open-label clinical trial that paclitaxel nano-formulation NK105 has better safety profile when treated for a 28-day cycle with significant decrease in peripheral sensory neuropathy (PSN) toxicity compared to conventional paclitaxel alone in metastatic/recurrent breast cancer patients. Further, they found NK105 (65 mg/m²) response rate is similar to paclitaxel (80 mg/m²) with better antitumor activity and less non-hematological toxicity in patients with solid tumors.⁶⁸

Irinotecan Hydrochloride Liposome [ONIVYDE®]

Pancreatic cancer is among the deadliest cancer types demanding effective therapy globally. Onivyde is an irinotecan phytochemicals conjugating liposomal nanoformulations. Drug irinotecan liposome injection approved for second-line treatment only in combination with 5-FU and LV after first-line treatment with gemcitabine. Irinotecan HCL liposome injection is encapsulated within a lipid bilayer liposome and upon activation by carboxylesterases reaction, converted to active SN-38 metabolite. This topoisomerase-1 inhibitor drug reversibly binds to the topoisomerase-1–DNA complex, causing DNA damage, cell cycle arrest leading to cell death. Wang-Gillam et al, in 2019, reported NAPOLI-1 study results which are a phase-III clinical trial including 417 patients from over 100 locations worldwide demonstrated Onivyde had better

tumor accumulation in the cytoplasm and improved overall survival rate to 6.1 months in advanced metastatic pancreatic cancer patients.⁶⁹ However, high cytotoxicity of the Onivyde drug has generated concerns about its safety.

Liposomal Vinorelbine Tartrate [Navelbine/NanoVNB[®]]

NanoVNB[®] contains PEGylated nano-liposomal vinorelbine (2 mg/mL), N-(methoxypolyethyleneglycolcarbamy)2000-1,2-distearoyl-sn-glycero-3-phosphoethanolamine (0.23 mg/mL), histidine, distearoyl phosphatidylcholine (4.45 mg/mL), cholesterol (1.45 mg/mL) and sucrose. This nano-drug has selective and superior tumor penetration efficacy including slow-release, longer stability, low toxicity, ten times higher plasma concentration (C_{max}), low plasma clearance (CL), superior half-life, and 1500 times higher AUC (area under the curve) compared to the free vinorelbine. A research report by Yang et al demonstrated that liposomal vinorelbine (NanoVNB[®]) infused at 2.2–23 mg/m² dose range once for every 14 days, show low plasma clearance, better pharmacokinetics with low toxic effects including low skin rash without grade 3–4 hematological toxicity, in patients suffering from refractory advanced solid tumors such as nasopharyngeal cancer, angiosarcoma, head and neck cancer, breast cancer, lung cancer, etc. Skin rash occurred at higher dose concentrations (23.0 mg/m²), recommending a dose of 18.5 mg/m² every 3 weeks for phase II clinical trials.⁷⁰

Vincristine Sulfate Liposome [Marqibo[®]]

Liposomal nano-formulation of vincristine sulfate (VSLI), composed of sphingosomal/cholesterol as solvent possesses curative anticancer properties and better pharmacokinetics compared to conventional vincristine alone. This drug accumulates passively into the tumor tissue and releases slowly the core drug into the tumor microenvironment, proven to have a better overall response rate. Liposomal formulation along with sphingomyelin reduces its toxic effect considerably; further, longer circulation time improves its therapeutic index. Based on these properties VSLI is prescribed for the treatment of clinically advanced Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL). Recently this nano-formulation of vincristine phytomolecules is under clinical trials for the treatment of several other cancer types, such as Hodgkin lymphoma, malignant melanoma, sarcoma, neuroblastoma.⁷¹

Liposomal 9-Nitrocamptothecin [L9-NC]

Aerosolized L-9-nitro-20(S)-camptothecin (L9-NC) is a liposomal nano-formulation of plant alkaloid camptothecin

derivative with potential anticancer effects. When used as an aerosol with a nebulizer, the advantages of this drug are readily systemic absorption with less toxicity profile and efficient anticancer activity through cell cycle arrest and apoptosis, as proven by Phase-I/II study in advanced pulmonary malignancies patients.⁷² L9-NC is currently under clinical trials for various cancer therapies such as endometrial cancer, Ewing's sarcoma, and lung cancer (Table 3).

Cyclodextrin-Based Polymer-Camptothecin Nanoparticle [CRLX101/NLG207]

Cyclodextrin-based polymer-camptothecin nanoparticle formulation has potent anticancer properties via cell cycle arrest and cell death. Preferentially this nano-formulations camptothecin accumulated in the target cancer tissues with less toxicity to the normal cells. Nano-camptothecin has a superior half-life of 24 hrs compared to the 2hrs of conventional drugs which makes it enable for prolonged sustained release of drugs to the cancer site.⁷³ Moreover, multiple phase-I/II trials for nano-camptothecin have proven its efficacy as cancer therapeutics. Recent reports demonstrated in a phase-II trial that nano-camptothecin drug conjugate has a better toxicity profile in locally advanced rectal cancer and gastroesophageal cancer patients.^{74,75}

Curcumin Liposome [Lipocurc[™]]

Liposomal nano-formulation of phyto-compounds such as curcumin polyphenol containing DMPC (14:0–1, 2-dimyristoyl-sn-glycero-3-phosphocholine) and DMPG (14:0–1, 2-dimyristoyl-sn-glycero-3-phosphorylglycerol), possess potential anticancer effects. When infused intravenously, the liposomal carrier increased curcumin plasma levels significantly in a dose-dependent manner in cancer patients. Moreover, upon dose withdrawal, drug clearance rate and the half-life is also shorter than healthy individuals.⁷⁶ In another phase-I clinical study on metastatic tumor patients, liposomal curcumin formulation (300mg/m², over 6h, for 8 weeks) has shown stable plasma concentration with a significant but temporary reduction in tumor markers such as PSA, CEA, CA 19–9. Additionally, liposomal curcumin has sphingosine kinase inhibitor activity, that warrants the use of liposomal curcumin monotherapy or in combination can reduce the recurrence of cancer and suitable for further clinical trials.⁷⁷ Altogether, these reports suggest that lipocurcumin is a safe drug and upon pre-treated, as intravenous administration produces ceramide, which reduces cancer markers significantly via cell cycle

arrest and apoptosis and has a better toxicity profile along with sustained drug release efficacy compared to curcumin alone.

Curcumin/Doxorubicin-Encapsulating Nanoparticle [IMX-110]

The phytomolecule-nanoparticle-conjugation formulation comprises of curcumin (Stat3/pan-kinase/NF-kB inhibitor) and a low amount of doxorubicin sheathed in nano-delivery conformity for enhanced tumor infiltration is an apoptosis inducer. To expand its phase Ib/IIa clinical trial from Australia to the US, six cohorts have shown no drug-related severe toxicity upon drug augmentation with a potent inhibitory effect against cancer resistance. If needed, this nano-drug can be tuned in such a way that it could be bound to multiple moiety targets, releasing enhanced drug loads in cancer sites or other preferred cell communities. This nano-drug has been approved in July 2019 for the treatment of refractory solid tumors encased with superior efficacy from the perspective of low cardiac toxicity compared to older prescribed formulations (Table 3).

Liposomal-Encapsulated Docetaxel [LE-DT]

Liposomal nano-formulation of docetaxel (ATI-1123/LE-DT) is used for the treatment of various cancer types. This liposomal nano-docetaxel formulation is less toxic, allowing the larger dose administration, enhanced drug solubility, reduces drug degradability, slow drug release/clearance, reducing side-effects and toxicity, thereby improving the overall anticancer efficacy against docetaxel alone. Liposomes are also effective to bring under control multidrug resistance (MDR) specifically mediated by P-glycoprotein (P-gp) and related MDR proteins.⁷⁸ A phase-I study of advanced solid tumor malignancy conducted by Mahalingam et al demonstrated that a liposomal encapsulated docetaxel exhibited favorable pharmacokinetics and stable disease response in 75% of patients. The maximally tolerated dose suggested being 90mg/m² over 1h for every 3 weeks when administered intravenously.⁷⁹ In another report by Deeken et al, a new nano-sized stable liposome encased with docetaxel using oppositely charged lipid and the drug had been administered on a dose ranging from 50–132mg/m² for 1–30 cycles on every 3 weeks to solid tumor patients. In this clinical trial, the nano-formulations of the drug found to be safe without significant toxicity like neuropathy or edema, in exception to the only toxicity recorded was neutropenia at higher dose concentrations (110 and 132 mg/m²), which was mitigated with peg-filgrastim co-administration. In

conclusion, this phase I study with 41% of clinical benefit suggests 85 mg/m² as a safe dose concentration for phase II clinical trial without the use of filgrastim for the effective treatment of advanced solid tumor malignancies.⁷⁸

Docetaxel Polymeric Micelle [Docetaxel-PM/NANOXEL-M]

Docetaxel polymeric micelle is a nano-formulation of phyto-drug docetaxel encased with an aqueous core of polymeric micelle, with active antineoplastic effect. This nano-drug is under phase-II clinical trials for the treatment of metastatic head and neck cancer and under phase-III clinical study for bladder cancer, esophageal squamous cell carcinoma (Table 3).

Docetaxel-Entrapped CriPec Nanoparticles [CriPec[®] Docetaxel/CPC634]

CPC634 is a nano-formulation of docetaxel adsorbed tuneable CriPec nanoparticles. A recent report of 2020, by Atrafi et al, demonstrated that CPC634 upon administration at 60mg/m² every 3weeks, shows better intra-tumoral accumulation lowering toxicity like neutropenia along with skin toxicity, due to slow release of the drug compared to the conventional one. Pharmacokinetics results revealed that this nano-docetaxel formulation has seven fold lower C_{max} and two fold higher half-life. It binds specifically to tubulin for inducing G2/M cell cycle phase arrest and apoptosis by reducing tumor burden in advanced solid tumor patients.⁸⁰ Another recent report the author demonstrated that CPC634 nanoparticles (75 mg/m², for 2 cycles) increased, sustained, and prolonged intratumoral concentration of drug docetaxel by 25%, lowering grade 3 and grade 4 neutropenia cases in solid tumor patients.⁸¹

Docetaxel Polymeric Nanoparticle Formulation [SYP-0709]

This drug is a formulation of polymeric nanoparticle having docetaxel core drug (SYP-0709/Docetaxel-PNP), with enhanced anticancer activity via cell cycle arrest compared to docetaxel alone. This agent not only inhibits cancer cell growth but also restricts vascular endothelial growth factor (VEGF). A phase-I clinical trial is currently ongoing using this nano-drug in patients with advanced solid tumors to evaluate its safety, pharmacokinetics, and maximum tolerated dose (Table 3).

Docetaxel-Loaded Nano-Pharmaceutical [CRLX301]

Docetaxel-loaded nano-pharmaceutical (CRLX301) is a tumor-targeted cyclodextrin-polyethylene glycol copolymer-conjugated nanoparticle-based formulation of docetaxel,

with minimized systemic toxicity and better tumor accumulation. Docetaxel-loaded nano-pharmaceutical can be uptaken by tumor cells via macropinocytosis and can be used in higher doses compared to docetaxel alone with sustained-release inducing cell cycle arrest and apoptosis. Interestingly, a recent report of 2020, explained nano-docetaxel drug binds to microtubule (MT) by inducing MT-drug-target engagement (DTE). Further, increases stabilization of MT with better treatment outcome as evident from MT-DTE score of CTCs (circulating tumor cells) extracted from peripheral blood of refractory solid tumor patients.⁸² In a Phase 1/2a clinical trial by Ben Markman et al suggested that nano-docetaxel (CRLX301) has an enhanced antitumor activity and acceptable toxicity profile when administered up to 6 cohorts on a dose ranging from 7.5 to 75 mg/m² every 3–1 weeks (up to 15 cycles). Nanoformulation enabled prolonged release of drug and better tumor penetration in patients with refractory advanced solid tumor malignancy such as head and neck cancer, cholangiocarcinoma and lung etc., as compared to the conventional drug. As per FDG-PET and CT scan report, a B-RAF mutant patient observed with tumor shrinkage and partial metabolic response, and other patients were observed with the stable disease having docetaxel induced anomalies. The maximally tolerated dose was suggested as 75 mg/m² for every 3 weeks of treatment.⁸³

Nanosomal Docetaxel Lipid Suspension [Doceaqualip]

NDLS is prepared by 'Nano Aqualip Technology, for better stability, improved pharmacokinetics, and low cytotoxicity to normal tissue. The nanosized NDLS (~100 nm) can readily pass through tumor tissue's leaky vasculature concealing it from the immune defense system. This drug has been approved in India for clinical use in breast cancer, gastric adenocarcinoma, hormone-refractory prostate cancer, and head and neck cancer patients, without any pre-medication of corticosteroids or antihistamines.⁸⁴ Recently, in 2019, Ramaswamy et al reported an excellent outcome of NDLS in a pregnant woman having breast cancer metastasized to lung and liver. The patient is given with NDLS, cyclophosphamide, and doxorubicin combinatorial drug for six cycles, show effectively reducing the disease burden without significant toxicity or hypersensitivity. Further, delivering a healthy child without any adverse effect on both mother and child.⁸⁴ Another clinical case reported by Radheshyam et al demonstrated herein, an adenocarcinoma patient with bone metastasis showed severe allergic reactions in treatment with docetaxel alone even after pre-treatment, with antihistamines and corticosteroids. Immediately the patient's treatment was replaced with NDLS (120 mg/m²), in combination with denosumab and filgrastim.

This NDLS formulation of docetaxel was well tolerated, without any adversity, and further continued for repeated 5 cycles. Reassessment with Ga-68 PSMA PET-CT scan reports (Figure 5) suggested improved health status having no metastases and no adversity. Furthermore, significant cancer regression has been detected with a considerable decrease in standardized uptake value (SUV) from 10.5 to 6.9 for the prostate and from 19.4 to 18.0 for skeletal lesions.⁸⁵ Also, a recent case study suggests that NDLS (Doceaqualip) is strongly effective in treating stage IIIB cervical cancer, achieves complete response (RECIST 1.1 criteria) without any significant adverse effects even without any pre-hypersensitivity medication. The patient had received concomitant radiotherapy along with chemotherapy using NDLS (120–100mg/m²) and carboplatin (AUC 6). After 2 consecutive cycles, grade II neutropenia observed, which was ameliorated by pegylated-filgrastim after every cycle of combinatorial chemotherapy. There was no evidence of residual mass inside the cervix along with no inflamed para-aortic nodes or internal iliac nodes observed after 4 cycles of treatment. Overall, after two years of follow-up, the patient did not develop any recurrence carcinoma, suggesting NDLS to be an excellent anticancer agent.⁸⁶

Conclusion and Future Perspectives

Given that cell cycle phase arrest and apoptosis play a critical role in the progression of cancer, its disruption by phytochemicals in a well-defined target specific molecular approach seems to be a promising strategy in regulating carcinogenesis. Though, so far treatments using chemically synthesized drugs have high toxic effects on the surrounding normal tissues inducing numerous severe side effects. Subsequently, alternative plant-based anticancer therapies are more effective and readily acceptable. Recent advancement in the areas of nanobiotechnology has proven to cure cancer with more potency and tissue-specific manner in conjugation with various nanoparticles and phytochemicals. Plant-based secondary metabolites such as flavonoids, phenolic compounds, alkaloids, flavanols, terpenes, steroids, flavonolignans, organo-sulfur compounds, and brassinosteroids have reported of destroying tumor cells by versatile ways, such as inducing cancer cell cycle arrest and enhancing apoptotic cell death process. Phytochemicals such as camptothecin, topotecan, irinotecan, etoposide, doxorubicin, paclitaxel, docetaxel, vinblastine, and vincristine, etc. are already in the global pharmaceutical market for various cancer treatments with superior anticancer potency. Consequently, strategic clinical trials can establish optimal anticancer

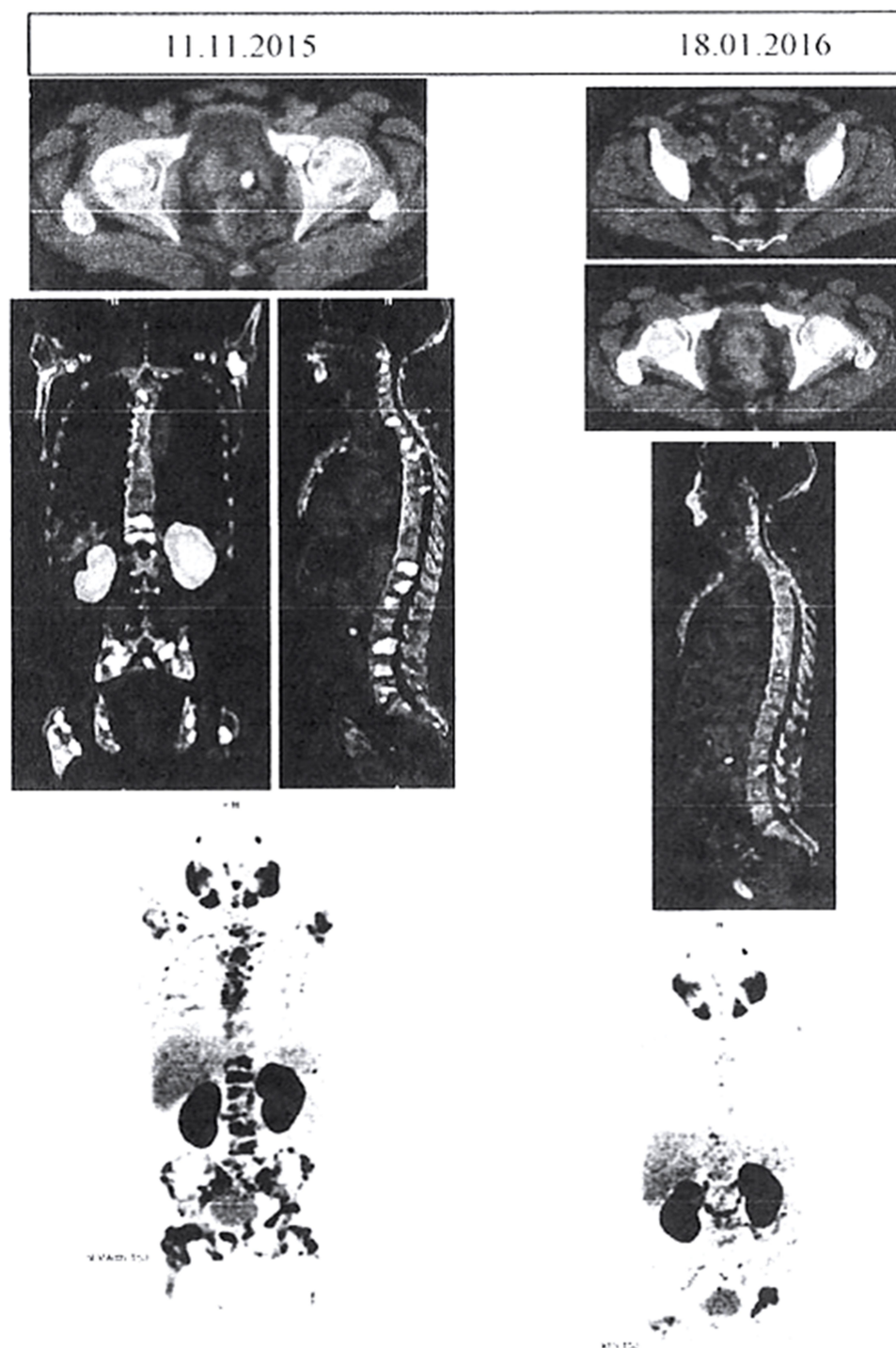


Figure 5 Comparative Ga-68 PSMA PET CT scans before and after the administration of Docequalip.

Notes: Left panel: Images obtained in November, 2015, showing post-TURP changes, small mild nodular hypermetabolism in the left posterior peripheral zone (likely representing residual prostatic disease) and extensive FDG-avid heterologous osteosclerotic lesions. Right panel: Images obtained in January, 2016, showing post-TURP changes, mild interval regression of the nodular hypermetabolism in the left posterior peripheral zone and morphologically stable heterogenous osteosclerotic lesions with internal regression of the metabolic activity. PSMA, prostate-specific membrane antigen; PET, positron emission tomography; CT, computed tomography; TURP, transurethral resection of the prostate; FDG, fluorodeoxyglucose. Adapted with permission from Atrafi F, Eerden R, van Hylckama Vlieg Met al Intratumoral Comparison of Nanoparticle Entrapped Docetaxel (CPC634) with Conventional Docetaxel in Patients with Solid Tumors. *Clinical Cancer Research*. 2020;26:clincanres.0008.2020.⁸¹ ©copy right (2020), Molecular and Clinical Oncology.

phytotherapy conditions and personalized treatment algorithms by utilizing advanced nanotechnology for the cost-effective, target-specific, and less toxic chemopreventive agents to counter global demands. The current chapter provides detailed knowledge of the cancer therapeutic phytomolecules approved by the Food and Drug Administration (FDA, USA) inclusive of phytobioactives presently on the clinical trials. Inline, detailed coverage is given to the newly emerging nano-phyto-formulations (FDA-approved) of target-specific cancer theranostics via cell cycle arrest and apoptotic pathways. This chapter provides comprehensive knowledge that alludes to paving a way for the advancement of cancer research and development.

Disclosure

The authors report no conflicts of interest for this work.

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