



RESURGENCE OF PHYTOMEDICINES: A PROMISING APPROACH FOR CANCER MANAGEMENT

Priyanka Dixit, Deepika Singh, Narendra Kumar Singh, Rajiv Gupta*

School of Pharmacy, BBD University, Lucknow-226 028 (U.P.) India.

*Corresponding author e-mail: rajiv961@rediffmail.com

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ABSTRACT

Cancer is a major cause of morbidity and mortality worldwide. It is the second only cause of mortality after cardiovascular disease. Conventional radiation and chemotherapies are associated with severe side effects in addition to being exorbitantly expensive. Phytomedicine derived from medicinal plants and their extracts along-with their isolated bioactive phytomolecules have been utilized by mankind since historical times to relieve their suffering and ailments. Many isolated bioactive phytochemicals and extracts of plants including single plant/part or poly-herbal preparations, used in traditional medicine are known for their safety, diverse healing properties and being economical to the user, that stands true for anticancer activities also. The present paper is a compilation of a comprehensive review of various available literature authentic sources of scientific information from institutions of high repute such as C.S.I.R. libraries, PubMed, Web of Science, Google Scholar, Scopus, and available traditional texts/ records associated with historical ethno-pharmacological knowledge, collected from indigenous medicinal plants specialists, with discussion being made on the therapeutic value of medicinal herbs and their phytomolecules in the treatment of various kinds of cancer patients they encounter. Relevant molecular mechanisms involved in the anticancer effects of these Phytomedicine are also discussed. The present review of literature survey demonstrates that the Phytomedicine have the potential for repurposing or repositioning in cancer therapy. Further studies are needed for exploring more plants, their active constituents, mechanism of anticancer action, mechanisms underlying additive, synergistic and antagonistic interactions for use as standard herbal medicine.

INTRODUCTION

Nature has a rich treatise of medicinal plants rich in phytochemicals which have been used since antiquity for various prophylactic and therapeutic purposes since the prehistoric era [1]. Previous studies have found that some of these traditionally mentioned plants have special significance in the management or treatment of cancer and may play a significant

role in form of the resistance of cancer cell proliferation, induction of cancer cell apoptosis, induction of autophagy, anti-angiogenesis, inhibition of cancer cell migration and invasion, etc. [2]. Cancer is defined the uncontrolled growth and multiplication of abnormal cells in the body. Some characteristics of cancer genesis include genomic instability, proto-oncogene

activation and tumor suppressor gene inactivation, epigenetic instability, apoptosis, telomerase activity, and angiogenesis [3]. Being the second biggest cause of morbidity and mortality in the world after cardiovascular illnesses, cancer has emerged as a significant health problem. The prevalence, mortality, and incidence of cancer are all increasing on a global scale. Global estimates for 2018 include 185 states, 36 different malignancies, 18.1 million new cases of cancer, and roughly 9.6 million deaths from cancer. About 1 in 6 fatalities worldwide are caused by cancer [4]. By 2030 and 2040, it is anticipated that there would be 24.1 million new cases of cancer annually [5]. The most prevalent cancer types that affect people worldwide include lung, breast, cervical, and prostate cancers. Out of all the different cancer kinds, female breast cancer is the most common cause of mortality in women, affecting one in every four of them [6].

Multiple cancer treatments such as chemotherapy, surgery, and radiotherapy are available but they have innumerable side effects quite painful and confined to treating one area only. Several plant-derived agents such as vincristine, etoposide, paclitaxel, and topotecan are among the most effective cancer chemotherapeutics currently available. In addition to terrestrial plants, marine environments, microbes and slime molds have yielded remarkable cancer chemotherapeutic agents [7]. Irrespective of these advances, cancer remains a leading cause of death worldwide undoubtedly; the prevention of cancer is highly preferable to treatment. Thus, alternative treatments against cancer are very much desired and desperately needed [3]. Phytomedicines offer a viable alternative to conventional cancer treatment because they include a variety of chemical components that are safe, effective, affordable, and widely accessible [4]. Numerous phytomolecules from medicinal products have been crucial in the discovery and development of novel anti-cancer medicines, which offer a particularly rich supply of biologically active molecules.

Due to the rising number of cancer survivors who employed the traditional system of medicine for their cancer treatment over the past 10 years, the adoption of medicinal plant products has significantly increased in both industrialized and developing countries [8]. In this review, we have attempted to focus on the preclinical studies conducted on the anticancer effects of some of the selected medicinal plants and their bioactive phytomolecules. Such review studies on medicinal plants can lead to the development of successful plant-derived chemicals as well as the therapeutic use of certain plants because phytomedicines made from plants and their phytoconstituents are often abundant, safe, and healthful.

2. Some promising medicinal plants with anti-cancer activity

Medicinal plants and plant-derived medicines play a key role in the primary health care system in the prevention and treatment of various diseases, including cancer. Taxol (*Taxus brevifolia*), vinblastine (*Catharanthus roseus*), vincristine (*Catharanthus roseus*), topotecan (*Camptotheca acuminata*), irinotecan (*Catharanthus roseus*), camptothecin (*Camptotheca acuminata*) as well as epipodophyllotoxins, are among the most potent and commonly used cytotoxic plant-derived substances in clinical practice. A single plant may contain one or more active compounds that interact synergistically with compounds from other plants to offer a combinatorial approach that would deliver an enhanced therapeutic effect. This combinatorial approach can also overcome resistance by reducing the activity of crosstalk cancer-activated signaling pathways. This endless supply of bioactive chemicals that medicinal plants offer varies by plant species, varietal types, geographical locations, and mechanism of action. Therefore, this study aims to provide detailed information about some of the promising medicinal plants, including family, part and extract used, active phytochemical, postulated mechanism of action, and evaluated anti-cancer activity as shown in Table 1 [7].

Table 1: List of some promising medicinal plants and their bioactive phytoconstituents with anticancer activity.

Plant and family	Plant part and extract used	Active phytoconstituent and proposed mechanism of anticancer action	Evaluated <i>In-vitro/In vivo</i> anticancer activity	Ref.
<i>Abrus precatorius</i> (Fabaceae)	Leaves Ethyl acetate	Stigmasterol hemihydrate and β -monolinolein By inducing apoptosis	MDA-MB-231 (breast cancer cells) and 7, 12-Dimethyl benz[a]anthracene (DMBA)-induced tumor in virgin female Sprague dawley rats	[9]
<i>Aegiceras corniculatum</i> (Aegicerataceae)	Stems and twigs Petroleum ether	Benzoquinones (2-hydroxy-5-ethoxy-3-nonyl-1,4-benzoquinone, 5- <i>O</i> -butyl-embelin, 2,5-dihydroxy-6-methyl-3-pentadecyl-1,4-benzoquinone, 2,5-dihydroxy-3-methyl-6-nonyl-1,4-benzoquinone, 2,5-dihydroxy-3-methyl-6-undecyl-1,4-benzoquinone, 2,5-dihydroxy-6-methyl-3-tridecyl-1,4-benzoquinone, 2-hydroxy-5-methoxy-3-nonyl-1,4-benzoquinone, 5- <i>O</i> -methylembelin, 5- <i>O</i> -methyl-rapanone, and 5- <i>O</i> -ethylembelin) By inducing cytotoxicity	HL-60 (human acute promyelocytic leukemia), Hep G2 (human hepatocellular cancer cells) BGC-823 (gastric cancer cells), and A2780 (human ovarian cancer cells)	[10]
<i>Ailanthus altissima</i> (Simaroubaceae)	Bark Dimethylsulf oxide	Ailanthone By inhibiting Hsp90 co-chaperone p23 and by modulating the expression of microRNAs	H-1975, A549 (human non-small cell lung cancer cell lines), 22Rv1, LNCaP, VCap (castration-resistant prostate cancer cell lines), and xenograft mice bearing Huh7 (human liver cell line)	[11]
<i>Aloe castellorum</i> (Asphodelaceae)	Leaf Methanolic	9-Octadecenoic acid By inducing apoptosis	HCT116 (colorectal cancer cell line)	[12]

<i>Aloe pseudorubroviolacea</i> (Asphodelaceae)	Leaves Methanolic	3-Dodecanol By inducing apoptosis	HCT116	[12]
<i>Alstonia scholaris</i> (Apocynaceae)	Leaf Hexane	Ursolic acid, betulinic acid, betulin, and 2 β ,3 β ,28-lup-20(29)-ene-triol By inhibiting proliferation	A549	[13]
<i>Andrographis paniculata</i> (Acanthaceae)	Aqueous	Andrographolide, neoandrographolide, deoxyandrographolide andropanoside, dehydroandrographolide, 5-hydroxy-7,8-dimethoxyflavone and 5-hydroxy-7,8-dimethoxyflavanone Due to anti-migratory and suppressive effects on metastasis-related factors (HER2, MMP2, MMP9, TM4SF3, CXCR4)	EC-109 (esophageal cancer cell line) and metastatic esophageal xenograft-bearing mice	[14]
<i>Anethum graveolens</i> (Apiaceae)	Seed Essential oil	Carvone, dillapiole and dihydrocarvone By causing cell cycle arrest and inducing apoptosis	Hep G2	[15]
<i>Annona muricata</i> (Annonaceae)	Fruit Methanolic and ethanolic	Acetogenins By inhibiting nicotinamide adenine dinucleotide oxidase enzyme	PACA-2 (pancreatic cancer cell line), A549, PC-3 (prostate cancer cell line) and Hep G2	[16]
<i>Arnica montana</i> (Asteraceae)	Root and rhizome Essential oil	2,5-Dimethoxy-p-cymene, 2,6-diisopropylanisole, thymol methyl ether, and p-methoxyheptano phenone By inducing apoptosis, necrosis, and autophagy	T98G (human glioblastoma multiforme cell line) and MOGGCCM (anaplastic astrocytoma cell line)	[17]
<i>Artemisia absinthium</i> (Asteraceae)	Aerial parts Methanolic	Quinic acid, cinnamic acid, rhoifolin, and malic acid By inducing apoptosis	DLD-1 (human colon cancer cell line), ECC-1 (endometrium cancer cell line), and HEK-293 (embryonic kidney cancer cell line)	[18]

<i>Asparagus officinalis</i> (Liliaceae)	Stem and spear n-butanol	Asparanin A (AA) By causing cell cycle arrest, by inducing apoptosis and by inhibiting PI3K/AKT pathway	Ishikawa (human endometrial cancer cell line), HEK293, and Xenograft mice bearing Ishikawa	[19]
<i>Atalantia monophyla</i> (Rutaceae)	Peel Hexane, ethyl acetate, and methanolic	Benzoyltyramines (atalantums) By causing cytotoxicity	HeLa (cervical cancer cell line), HCT116, and MCF-7 (breast cancer cell line)	[20]
<i>Azadirachta indica</i> (Meliaceae)	Leaf Ethanolic	Azadirachtin and nimbolide By inducing apoptosis	KB, ORL 48, SCC-131, SCC-4, Cal-27, HSC-3 (oral cancer cell lines) and DMBA-induced tumor in hamster buccal pouch	[21]
<i>Basella rubra</i> (Basellaceae)	Fruit Aqueous and methanolic	Betalains, phenols, and flavonoids By inducing apoptosis	SiHa (cervical cancer cell line)	[22]
<i>Caesalpinia pulcherrima</i> (Fabaceae)	Leaf Petroleum ether, chloroform, ethyl acetate, and methanolic	Phenols and flavonoids By inducing apoptosis	HCT-116	[23]
<i>Cassia angustifolia</i> (Fabaceae)	Leaf Methanolic and ethanolic	Flavonoids (quercimeritrin, scutellarein, and rutin) By inhibiting proliferation, causing arrest of cell cycle and by inducing apoptosis	MCF-7, HeLa, and Hep2 (human larynx cell line)	[24]
<i>Cassia tora</i> (Fabaceae)	Leaf Ethanolic	Friedelin By inducing apoptosis	HeLa and HSC-1(human skin cancer cell line)	[25]
<i>Cissus quadrangularis</i> (Vitaceae)	Stem Ethanolic	Stigmast-4-en-3-one and octadecanoic acid By inducing apoptosis and upregulating p53 gene	KB	[26]
<i>Colocasia esculenta</i> (Araceae)	Corm Aqueous	Polysaccharides By immunostimulation	Yac-1 (T-cell lymphoma) and lung metastasis via inoculation of B16BL6 melanoma cells into syngenic BALB/c mice	[27]

<i>Conyza blinii</i> (Compositae)	Aerial parts Methanolic and ethanolic	Triterpenoidal saponins By modulating MAPK/TGF- β /Nrf2 signaling pathways	HeLa and xenograft mice bearing HeLa	[28]
<i>Cordia dichotoma</i> (Boraginaceae)	Leaf Methanolic	Flavonoids By inducing apoptosis and scavenging free radicals	PC3	[29]
<i>Crocus sativus</i> (Iridaceae)	Stigma Hydroalcoholic	Crocetin and Crocin By causing cell cycle arrest and by modulating the expression of N- cadherin, beta- catenin, and E- cadherin	PC3, 22Rv1, and xenografted mice bearing PC3, 22Rv1	[30]
<i>Cudrania tricuspidata</i> (Moraceae)	Stem Methanolic	Chlorogenic acid, (+)- catechin, caffeic acid, phloretic acid, veratric acid, hesperidin, quercetin, and naringenin. By causing apoptosis and through repression of HPV-16 oncoproteins E6 and E7 as well as <i>via</i> alteration of protein levels of p53 and p- pRb	HPV-16-positive SiHa, CaSki (cervical cancer cells), and HaCaT (human normal keratinocytes)	[31]
<i>Cuminum cyminum</i> (Apiaceae)	Fruit Ethyl acetate and hexane	Flavonoids (luteolin, apigenin, luteolin- 7- O-glucoside, apigenin-7-O- glucoside) By inducing apoptosis and causing the cell cycle arrest	MCF-7 and MDA-MB- 231	[32]
<i>Curcumis sativus</i> (Cucurbitaceae)	Leaf Methanolic and acetone	Alkaloids, glycosides, steroids, saponins, and tannins By inducing apoptosis	MCF-7 and HeLa	[33]
<i>Cynara cardunculus</i> var. <i>scolymus</i> (Asteraceae)	Bract and receptacle Ethanolic	Phenols and flavonoids By causing cytotoxicity and scavenging free radicals	HepG2, MCF-7, and HCT-116	[34]

<i>Dodonaea viscosa</i> (Sapindaceae)	Flower, leaf, stem and root Ethanolic and ethylacetate	Polyphenols (rutin, vanillic acid, coumaric acid, ferulic acid, gallic acid, syringic acid, cinnamic acid, gentisic acid, catechin, caffeic acid, apigenin and myricetin) By inhibiting proliferation and inducing cytotoxicity	Brine shrimp lethality assay, HepG2, and THP-1 (human leukemia cell line)	[1]
<i>Gambogia genera</i> (Guttiferae)	Pericarp Dimethyl sulfoxide	Garcinol By suppressing p300 and TGF- β 1 signaling pathways	KYSE 150, KYSE 450 (human oesophageal cancer cell lines) and pulmonary metastasis assay in BALB/c nude mice	[35]
<i>Ginkgo biloba sarcotestas (GBS)</i> (Ginkgoaceae)	Fruit Petroleum ether	2-Hydroxy-6-tridecylbenzoic acid By the activation of aryl hydrocarbon receptor pathway	MDA-MB-231 and mouse 4T1 (triple-negative breast cancer cell line)	[36]
<i>Glycyrrhiza glabra</i> (Fabaceae)	Root Aqueous	AK027294 By inhibiting the expression of lncRNA and by inducing apoptosis	C666-1 (nasopharyngeal carcinoma cell line)	[37]
<i>Glycyrrhiza inflata</i> Batalin (Fabaceae)	Roots Dimethyl sulfoxide	Licochalcone C By inducing apoptosis and causing cell cycle arrest.	KYSE 30, KYSE 70, KYSE 410, KYSE 450, and KYSE 510 (human oesophageal cancer cell lines)	[38]
<i>Hedera nepalensis</i> (Araliaceae)	Leaves Ethanolic	Hederagenin 3-O- α -L-arabinopyranoside and Pulsatilla saponin By inducing apoptosis	A549	[39]
<i>Helicteres isora</i> (Sterculiaceae)	Whole plant Hexane, ethanol and water	Flavonoids By inducing cytotoxicity	HEP-3B (human hepatoma cell line), HeLa-B75 (human cervical cancer cell line), HL-60, and PN-15 (renal cell carcinoma)	[40]
<i>Humboldtia unijuga</i> (Fabaceae)	Root Hexane and chloroform	Erythrodiol-3-acetate (HU-1) and 2,4-di-tert-butylphenol (HU-2) Through activation of caspase 7 and p53 gene	A431 (skin cancer cell line) and MCF-7	[41]
<i>Inula helenium</i> (Asteraceae)	Root Ethanol	Isoalantolactone, alloalantolactone, and alantolactone	PANC-1 and SW1990 cells (pancreatic cancer cell lines)	[42]

		By inducing apoptosis		
<i>Lannea barteri</i> (Anacardiaceae)	Leaf, stem and bark Dichloromethane, methanolic, and aqueous	Terpenoids and steroids By inducing apoptosis and causing cell cycle arrest	5637 (human bladder cancer cell line), KYSE 70 (human oesophageal cancer cell line), SiSo (human cervical cancer cell line), and HepG2	[43]
<i>Lavandula bipinnata</i> (Lamiaceae)	Whole plant Hexane, ethanol and water	Flavonoids By inducing cytotoxicity	HEP-3B, HeLa-B75, HL-60, and PN-15	[40]
<i>Litsea elliptica</i> (Lauraceae)	Leaves Methanolic and ethanolic	Flavonoids, terpenes, alcohols, fatty acids, and their methyl esters and vitamin E By inducing apoptosis	A549	[44]
<i>Matricaria recutita</i> (Asteraceae)	Flower Ethanolic	Phenols and flavonoids By inhibiting angiogenesis and metastasis	HepG2	[45]
<i>Mimusops elengi</i> (Sapotaceae)	Flower Ethylacetate	N2-Methyl aurantiamide (dipeptide) By inducing apoptosis	HL-60	[46]
<i>Nigella sativa</i> (Ranunculaceae)	Seed	Proteins By inducing apoptosis	MCF-7	[47]
<i>Nauclea latifolia</i> smith (Rubiaceae)	Stem bark Methanolic	Alkaloids, flavonoids, glycosides, saponins, tannins and coumarins By causing cytotoxicity	MCF-7, RD (Skeletal muscle cancer cell line)	[4]
<i>Oliveria decumbens</i> (Apiaceae)	Aerial parts Essential oil	Thymol, carvacrol, p-cymene, and γ -terpinene By promoting apoptosis and through immunomodulatory effects	4T1, L929 (mouse 120 normal fibroblast cell line), and 4T1 tumor model in BALB /c mice	[48]
<i>Origanum minutiflorum</i> (Labiatae)	Leaf Essential oil	Carvacrol By inducing apoptosis	MCF-7, A549 and HepG2	[49]
<i>Paeoniae Radix</i> (Paeoniaceae)	Aqueous and ethanolic	Oleanolic acid and hederagenin By inhibiting aurora kinase activity	A549	[50]
<i>Panax notoginseng</i> (Araliaceae)	Root Ethanol	Notoginsenoside and ginsenoside By decreasing IL- 4 (Interleukin- 4) secretions, arresting the cell cycle at G ₂ /M phase, and inducing apoptosis	PCa (Prostate cancer) cells, LNCaP and 22Rv1 cells	[51]

<i>Paris forrestii</i> (Melanthiaceae)	Rhizome Ethanolic and ethylacetate	PCT3 (total saponins from <i>Paris forrestii</i>) Polyphillin D, paris saponin Tg, By modulating the expression of mRNA, lncRNA and by inducing apoptosis	PC3, LNCaP and DU145 (human prostate cancer cell line), and RWPE (human normal prostate epithelial cell line)	[52]
<i>Phoenix dactylifera</i> (Arecaceae)	Heart Ethanolic	Polyphenols By inducing apoptosis	MCF-7, Caco-2 (human colon cancer cell line), HeLa and doxorubicin- induced organ toxicity in a rat model	[53]
<i>Phyllanthus amarus</i> (Acanthaceae)	Ethanolic	Phyllanthin, hypophyllanthin, gallic acid, niranthin, geraniin, phyltetralin, isoltetralin, corilagin and ellagic acid <i>Via</i> induction of apoptosis	HCT116	[54]
<i>Piper regnellii</i> (Piperaceae)	Leaves Dichloromet hane	Eupomatenoid-5 By inhibiting proliferation and growth	UACC-62 (human melanoma cell line), MCF-7, 786-0 (kidney cancer cell line), NCI- H460 (lung cancer cell line), PC-3, OVCAR-3 (ovarian cancer cell line), HT-29 (colon cancer cell line), K-562 (leukemic cell line) and Ehrlich solid tumor on BALB/c mice	[55]
<i>Piper cubeba</i> (Piperaceae)	Hydroalcohol ic extract	Lignans (cubebin, dihydrocubebin, ethylcubebin, hinokinin and methylcubebin) <i>Via</i> alteration in the expression of genes and proteins involved in inflammation	Hep2 and SCC-25 (oral squamous carcinoma cells) and normal fibroblasts	[56]
<i>Pittosporum angustifolium</i> Lodd. (Pittosporaceae)	Leaf, stamen and flower Aqueous and methanolic	Chlorogenic acid, p- coumaric acid, caffeic acid, t-ferulic acid and rutin. By inducing cytotoxicity	HeLa and HT29 cells	[7]
<i>Rauvolfia reflexa</i> (Apocynaceae)	Bark Hexane and methanolic	Reflexin A, macusine B and vinorine By inducing apoptosis	HCT-116	[57]

<i>Rhododendron luteum</i> (Ericaceae)	Aerial parts Ethyl acetate, methanolic, and aqueous	Phenols and flavonoids By inhibiting proliferation and inducing cytotoxicity	A549	[58]
<i>Rumex vesicarius</i> (Polygonaceae)	Root, stem, leaf, and flower Methanolic, chloroform, hexane, and ethyl acetate	Propanoic acid, 2,3- bis[(trimethylsilyl)oxy]-, trimethylsilyl ester, butanedioic acid, bis(trimethylsilyl) ester, butane, and 1,2,3- tris(trimethylsiloxy) By inhibiting angiogenesis	MCF7, Caco-2, Lovo (human colon cancer cell line), and HepG2	[59]
<i>Sansevieria roxburghiana</i> (Asparagaceae)	Rhizome Ethyl acetate	Gallic acid By inhibiting proliferation and inducing cytotoxicity	HCT-116, HeLa, and MCF-7	[60]
<i>Senna velutina</i> (Fabaceae)	Root Ethanolic	Catechin, anthraquinone, and piceatannol By inducing apoptosis and causing cell cycle arrest	B16F10-Nex2 (Melanoma cell line) and subcutaneously injected B16F10-Nex2 in C57BL/6 mice	[61]
<i>Sisymbrium irio</i> (Brassicaceae)	Aerial parts n-Hexane	β -Sitosterol, stigmasterol and β - sitosterol- β -d- glucoside By inducing cytotoxicity	MCF-7, HCT-116 and HepG2	[62]
<i>Soymida fembrifuga</i> (Miliaceae)	Whole plant Ethanol	Phenolic compounds By inducing cytotoxicity	HEP-3B, HeLa-B75, HL-60, and PN-15	[40]
<i>Tagetes erecta</i> (Asteraceae)	Leaf Aqueous	Hexadecanoic acid, linolenic acid, quinic acid, coumaran, and β -stigmasterol By inducing apoptosis	EAC (Ehrlich ascites carcinoma) induced solid tumor model in Swiss albino mice and Hep2	[63]
<i>Taxus Yunnanensis</i> (Taxaceae)	Wood Aqueous	α -Conidendrin By inducing apoptosis	MCF-7 and MDA-MB- 231	[64]
<i>Terminalia bellirica</i> (Combretaceae)	Fruit	Gallic acid By scavenging free radicals and inducing apoptosis	SCC-25, SCC-4, Cal-33 (tongue squamous cell carcinoma), FaDu (pharynx squamous cell carcinoma), and Hep2	[65]
<i>Tinospora cordifolia</i> (Menispermaceae)	Whole plant Ethanolic	Phenolic compounds By inducing cytotoxicity	HEP-3B, HeLa-B75, HL-60, and PN-15	[40]
<i>Tridax procumbens</i> (Asteraceae)	Leaf Methanolic, ethanolic,	Alkaloids, carbohydrates, polyphenols, and	A549 and MCF-7	[66]

	chloroform, and water	tannins By inducing cytotoxicity		
<i>Trillium tschonoskii</i> (Trilliaceae)	Root and rhizome Ethanolic	Paris saponin VII By inducing apoptosis	NCI-H1299, NCI-H460 (human non-small cell lung cancer cell lines) and xenograft model of nude mice (BALB/c) lung cancer cells (A549)	[67]
<i>Urceola huaitingii</i> (Apocynaceae)	Stem	Parameritannin A-2 and proanthocyanidins By inducing apoptosis and by inhibiting PI3K/ AKT, ERK1/2, and p38 cell signaling pathways	HGC27 (gastric cancer cell line)	[68]
<i>Valeriana jatamansi</i> (Valerianaceae)	Root and rhizome	Valtrate By inducing apoptosis and by causing cycle arrest at the G ₂ /M stage	MCF-7, MDA-MB-231, and MCF-10A (human breast cancer cells)	[69]
<i>Vernonia amygdalina</i> (Asteraceae)	Leaf n-hexane, ethylacetate, and ethanolic	Ingenol-3-angelate, chlorogenic acid, 4-methoxycinnamic acid, apigetrin, apigenin, luteolin, diosmetin, baicalin, rhoifolin, scutellarin, 7-hydroxycoumarin, 4-methylumbelliferon and, and 4-methylumbelliferyl glucuronide <i>Via</i> induction of apoptosis, enhanced cell accumulation at G ₂ /M phase of cell cycle, and inhibition of expression of PI3K and mTOR pathways	4T1	[70]
<i>Vernonia leopoldi</i> Vatke (Asteraceae)	Leaf Ethyacetate	Sesquiterpene lactones (11 β ,13-dihydrovernoldalol, vernomenin, vernolepin, and 11 β ,13-dihydrovernoldalin) and flavonoids (apigenin, eriodyctiol, and luteolin)	MCF-7, MCF-10A and JIMT-1 (breast cancer cells)	[71]

		By inhibiting aldehyde dehydrogenase expressing cancer stem cell sub-population and TNF- α -induced translocation of NF- κ B to the cell nucleus		
<i>Withania coagulans</i> (Solanaceae)	Fruit Methanolic	Withaferin A By inducing apoptosis	MDA-MB-231 and Vero (kidney cancer cell line)	[72]
<i>Wrightia tinctoria</i> (Apocynaceae)	Stem bark Petroleum ether and ethyl acetate	Lupeol and β -sitosterol By causing apoptosis	MCF-7 and HeLa	[73]
<i>Zingiber striolatum</i> (Zingiberaceae)	Rhizome Essential oil	β -phellandrene, sabinene, b-pinene, geranyl linalool, terpinen-4-ol, a-pinene, and crypton By causing cytotoxicity	K562 (human leukemic cell line), A549, and PC-3	[74]
<i>Zea mays</i> (Poaceae)	Leaf Methanolic	Phenols and Flavonoids By inducing oxidative stress and apoptosis	Hep2	[75]

3. Some promising phytomolecules for the management of cancer

Phytomolecules are secondary metabolites produced by plants, which are generally divided into different classes such as polyphenols, terpenoids, alkaloids, nitrogenous compounds, carbohydrates, lipids, phytosterols, and carotenoid [76]. Due to the significant biological activities, the intake of phytochemicals is also helpful for the prevention and treatment of various diseases, including cancer. Many clinical studies have described the mechanism of inhibition of phytochemicals on cancer cells in three ways: induction of apoptosis, inhibition of mitosis, and promotion of carcinogen metabolism. In addition, phytochemicals may enhance antioxidant and anti-inflammatory abilities by reducing pro-inflammatory factors [77]. These compounds are useful in the treatment of cancer because of their individual, additive, or synergistic health-improving effects. Such phytochemical study of the extracts and identification of compounds are important for screening new lead compounds for new drug development [78]. In connection with this review, a great

deal of information was gathered on the pre-clinical efficacy of several phytochemicals, as follows:

3.1. Sulforaphane

Sulforaphane is a naturally occurring organosulfur compound derived from cruciferous vegetables such as broccoli and cabbages. It has been tested against a wide range of cancers, such as colon, breast, skin, stomach, and prostate cancer. Sulforaphane principally shows its anticancer effect through serving as an anti-oxidant, activation of the Nrf2-Keap1 signaling pathway, increasing the activity of phase II detoxifying enzymes, causing apoptosis, and halting the cell cycle in tumor cells. In a study conducted on breast cancer stem cells, sulforaphane has been found to inhibit the self-renewal, proliferation, and differentiation of breast cancer cells by inhibiting Wnt/beta-catenin self-renewal pathway [79]. Sulforaphane has been demonstrated to act in colon cancer cells mainly by activating the tumor suppressor gene p53 and by triggering apoptosis through the activation of the mitochondrial-caspase-dependent apoptotic pathway [80]. In a study conducted on human prostate cancer (PC-3)

cells, sulforaphane has been found to inhibit NF- κ B transcriptional activation and expression of vascular endothelial growth factor (VEGF), cyclin D1, and Bcl-xL genes [81].

3.2. Luteolin

Luteolin is a flavonoid found naturally in plants such as *Apium graveolens*, chrysanthemums, and carrots. Luteolin has been reported for breast, colon, pancreas, lung, stomach, cervical, and prostate cancers. It exhibits anticancer effects by inhibiting tumor cell proliferation, metastasis and angiogenesis, removing carcinogens, arresting cell cycle, inhibiting cyclin-dependent kinases, and inducing apoptosis. Numerous studies have shown that luteolin inhibits the proliferation of both androgen-sensitive and androgen-independent cell lines by causing apoptosis in prostate cancer cells (PC3 and LNCaP) [82]. Another study suggested that luteolin inhibits cell proliferation in mouse hepatoma cells (HepG2) *via* a caspase-mediated apoptotic pathway [83]. In human breast cancer cell lines, luteolin causes apoptotic cell death by activating the enzymes ERK (extracellular signal-regulated kinases) and p38 [84].

3.3. Apigenin

Apigenin is a natural flavone found in abundance in plants such as parsley, grapes, and *Moringa peregrina*. Apigenin showed antitumor activity against breast, colon, lung, liver, skin, and prostate cancer. Apigenin demonstrated potent antitumor effects through multiple mechanisms, such as triggering apoptosis of cancer cells, inducing cell cycle arrest, suppressing metastasis, and activating the immune response. Signaling pathways modulated by apigenin include PI3K/AKT, MAPK/ERK, JAK/STAT, NF- κ B, and Wnt/catenin signaling pathways. The ability of apigenin to suppress cancer cell migration, invasion, and metastasis by regulating the NEDD9/Src/AKT cascade has been demonstrated in colorectal cancer cell lines DLD1 and SW480 [85]. Apigenin inhibited cell proliferation and migration in an orthotopic colorectal cancer model by upregulating transgelin and suppressing matrix metalloproteinase-9 (MMP-9)

expression by decreasing AKT phosphorylation [86].

3.4. Curcumin

Curcumin, a natural polyphenol, is the main phytoconstituent of turmeric, *Curcuma longa* L. Curcumin has proven anti-cancer effects against prostate, breast, colon, and pancreatic cancer. In addition to triggering apoptosis, curcumin also affects or inhibits the production of some cytokines, enzymes, and growth factors, including MAPK, EGF, NF- κ B, PKD1, COX-2, STAT3, and TNF. Curcumin was analyzed in MDA breast cancer cells with the genes encoding metastatic matrix metalloproteinases (MMPs) and tissue anti-metastatic inhibitors of metalloproteinases (TIMPs). The study showed that curcumin inhibited MMP-2 and MMP-9 while increasing the expression of TIMP1 and TIMP4 in breast cancer cells, which helps to control cell metastasis [87]. By interfering with several cellular signaling pathways, including nuclear factor (NF- κ B), epidermal growth factor (EGFR), and mitogen-activated protein kinase (MAPK), curcumin has been shown in numerous studies to be an effective drug to induce apoptosis and suppress the proliferation of prostate cancer [88].

3.5. Crocetin

Crocetin is a natural apocarotenoid found in the saffron flower, *Crocus sativus* L. The mechanisms underlying crocetin's chemopreventive activity in cancer include antioxidant activity, apoptosis of cancer cells, modulation of the immune system, cell cycle progression, and tumor metabolism, as well as stimulation of cell-to-cell communication. Treatment with crocetin inhibits colon cancer cell (DU-145) proliferation by downregulating the genes HMGB1, IL-6, and IL-8 involved in inflammation and by suppressing the expression of NF- κ B, VEGF, and MMP-9 in DU-145 cells [89]. Crocetin has also been studied for human lung cancers (A549), where it was found to induce apoptosis through the activation of caspase-dependent signaling pathways [90].

3.6. Cyanidin

Cyanidin is a pigment derived from blackberries, blueberries, and cherries. Cyanidin was examined for its

antiproliferative activity using DU145 and LnCap human prostate cancer cell lines and was found to have antiproliferative effects by activating caspase-3 and inducing p21 protein expression [91]. In a study conducted cyanidin isolated from mulberry was found to induce apoptosis in breast cancer cells (MDA-MB-453) *via* caspase-3 cleavage and DNA fragmentation [92]. Cyanidin has been demonstrated to have anticancer effects in human colon cancer cells (HCT-116 and HT-29) by impairing immunological checkpoints [93]. Cyanidin has also been shown to be effective against skin cancer cell lines (HaCaT), where it exerts its effects by scavenging free radicals and inhibiting COX-2 expression [94].

3.7. Epigallocatechin-3-gallate

Epigallocatechin-3-gallate constitutes the phytoconstituent of green tea. Epigallocatechin shows anticancer activity by multiple mechanisms such as by acting as an antioxidant, inhibiting tumor cell proliferation, metastasis, angiogenesis, inhibiting nuclear factor- κ B signaling pathways, inhibiting enzymes protein kinases, and DNA methyltransferases, inhibiting anti-apoptotic protein Bcl-xL and thereby upregulating apoptosis. Epigallocatechin-3-gallate has been reported for its chemoprotective and anti-invasive effect against cholangiocarcinoma cells (HuCC-T1) where it shows its effect through the activation of the mitochondrial apoptotic pathway [95]. Epigallocatechin-3-gallate has been studied against renal carcinoma cells where it shows its effect *via* inhibiting matrix metalloproteinase-2 and metalloproteinase-9 [96]. In human prostate cancer cells (PC-3) epigallocatechin-3-gallate inhibits vasculogenic mimicry *via* decreased expression of Twist/VE-Cadherin/AKT Pathway [97].

3.8. Fisetin

Fisetin a naturally occurring flavone is a bioactive constituent present in plants such as strawberries, apples, and grapes. Fisetin exerts its anticarcinogenic effect by inhibiting proliferation, growth, and metastasis in cancer cells, inhibiting angiogenesis, and by inducing apoptosis. Fisetin has been studied for pancreatic cancer cells (PANC-1 cells) where

it acts by inducing apoptosis through the activation of mitochondrial stress-dependent pathways [98]. Fisetin reported to inhibit the proliferation of human laryngeal cancer cells (TU212) *via* activation of apoptosis, inhibition of ERK1/2, and AKT/NF- κ B/mTOR signaling pathways [99]. Fisetin was also found to suppress the growth and metastasis of renal cell carcinoma (RCC) *via* inhibition of CTSS (Cathepsin S) and ADAM9 (disintegrin and metalloproteinase 9) through MEK/ERK signaling pathways [100].

3.9. Genistein

Genistein a naturally occurring flavone is a phytoconstituent present in plants such as soybeans, Psoralea, and *Flemingia vestita*. Genistein shows cytotoxicity *via* multiple mechanisms such as inhibiting the production of free radicals, blocking angiogenesis, and uncontrolled cell proliferation, and inhibiting the enzyme tyrosine kinase. Genistein has been proved as a potent anticancer agent against colon cancer cells (HT-29) through the reversal of Epithelial-mesenchymal transition (EMT) *via* suppression of the Notch1/NF- κ B/slug/E-cadherin pathway [101]. In another study, genistein was reported as a promising phytoconstituent against hepatocellular carcinoma cell line (Hepa1-6) where it acts by inhibiting proliferation and by inducing apoptosis [102].

3.10. Imperatorin

Imperatorin is a coumarin that is obtained naturally from plants like *Angelica sinensis*, *Citrus maxima*, and *Eugenia jambolana*. Through a variety of mechanisms, including inducing apoptosis, triggering cell cycle arrest, and obstructing cell migration, imperatorin has been shown to have anticancer action in many cancer cell lines. Additionally, it was discovered that in gastric and melanoma cancer cell lines, imperatorin was a key modulator of apoptotic signaling *via* the PI3K/AKT pathways. According to several reports, imperatorin treatment increases the expression of death receptors (DR4 and DR5) in the lung cancer cell lines (A549 and PC9) as well as Bax levels in glioma carcinoma, which are responsible for cell death. Additionally, imperatorin treatment of HL-60 cells causes mitochondrial cytochrome c to be released into the

cytoplasm, activating caspase-9 and caspase-3 [103].

4. CONCLUSION

Throughout the world, the traditional system of medicine particularly phytomedicines have played a vital role in maintaining the health systems of suffering mankind since antiquity, and is used to manage and treat various diseases without or with minimal toxic effect. Herbal plants are often used as a natural remedy to cure various health problems including cancer, diabetes mellitus, heart diseases, hypertension, etc. Plants rich in bioactive phytomolecules such as alkaloids, flavonoids, tannins, and polyphenols have been used to cure illnesses because of their various pharmacological properties. India is always known to be a rich depository of medicinal plants and various forms of herbal medicine practices are considered as “living tradition”. The review mainly summarizes the prominent Indian medicinal plants, their extract, and their corresponding pharmacological properties as anti-cancer. The significance of this review is aimed to provide a detailed and collective scientific evaluation of the key phytocompounds and their pharmacological action for the possible development of new ethnomedicine in the future. Since time immemorial nature has influenced the mankind, who have inherited the treasures of traditional Indian medicinal knowledge from its traditional texts. The incidence of cancer in India has increased among various types of malignancies. We studied and reviewed the reports published in the reputed national and international journals, with focus on Indian medicinal plants that are extensively used and had been scientifically explored and investigated for their efficacy and safety profiles based on *in vitro* and *in vivo* studies and clinical trials. The reviewed data were critically analyzed, compiled following a thorough literature search to identify mainstream references collected from C.S.I.R. institute libraries, PubMed, Web of Science, Google Scholar, Scopus databases, and records associated with historical ethnopharmacological knowledge, collected from indigenous residents and local medicinal plants specialists. It is worthwhile to mention here that many medicinal plants

literature that were searched and reviewed, seemed to be quite promising considering their phytochemicals profile, and thus the authors hereby also recommends that they may further be explored for the Repurposing concept for managing other diseases. In this manuscript the authors had analyzed the huge amount of available information related to the medicinal plants particularly from India along-with anticancer leads thereby highlighting the most promising species and the isolated bioactive compounds. The present review is an attempt by authors that would serve as a ready reference for future researchers in the field of cancer management with the help of natural products.

Conflict of interest

The authors declare that there are no conflicts of interest associated with this publication.

Credit authorship contribution statement

Priyanka Dixit: Collection and analysis of data, draft manuscript preparation. **Deepika Singh:** Proof reading of draft manuscript and suggestions. **Narendra K Singh:** Critical suggestions for improvement of manuscript, proof reading of manuscript. **Rajiv Gupta:** Idea, Conceptualization & Final proofreading. The authors would like to thank the Librarian, Central Drugs Research Institute - C.S.I.R. (C.D.R.I.-C.S.I.R), Lucknow, for all assistance provided during the literature search. The corresponding author is also thankful to AICTE-MODROBS project grant (F. No. 8024/RID/BOR/MOD-458/2009-10).

REFERENCES

1. Malik MN, Haq IU, Fatima H, Ahmad M, Naz I, Mirza B, et al. Bioprospecting *Dodonaea viscosa* Jacq.; a traditional medicinal plant for antioxidant, cytotoxic, antidiabetic and antimicrobial potential. *Arab J Chem* 2022;15(3):103688.
2. Alqarni AA, Alamoudi AA, Allam RM, Ajabnoor GM, Harakeh SM, Al-Abd AM. The influence of antioxidant dietary-derived polyphenolic combination on breast cancer: Molecular study. *Biomed Pharmacother* 2022;149:112835.
3. Pathak MP, Pathak K, Saikia R, Gogoi U, Ahmad MZ, Patowary P, et al. Immunomodulatory effect of mushrooms and their bioactive compounds in cancer:

A comprehensive review. *Biomed Pharmacother* 2022;149:112901.

- 4. Charles-Okhe O, Odeniyi MA, Fakeye TO, Ogbole OO, Akinleye TE, Adeniji AJ. Cytotoxic activity of crude extracts and fractions of African peach (*Nauclea latifolia* smith) stem bark on two cancer cell lines. *Phytomed Plus* 2022;2(1):100212.
- 5. Madia F, Worth A, Whelan M, Corvi R. Carcinogenicity assessment: Addressing the challenges of cancer and chemicals in the environment. *Environ Int* 2019;128:417-29.
- 6. Rawat A, Reddy AV. Recent advances on anticancer activity of coumarin derivatives. *EJMEECH Reports* 2022;5:100038.
- 7. Mani J, Johnson J, Hosking H, Walsh K, Neilsen P, Naiker M. *In vitro* Cytotoxic Properties of Crude Polar Extracts of Plants Sourced from Australia. *CCMP* 2022;2(1):100022.
- 8. Khan S, Hussain A, Attar F, Bloukh SH, Edis Z, Sharifi M, et al. A review of the berberine natural polysaccharide nanostructures as potential anticancer and antibacterial agents. *Biomed Pharmacother* 2022;146:112531.
- 9. Sofi MS, Sateesh MK, Bashir M, Ganie MA, Nabi S. Chemopreventive and anti-breast cancer activity of compounds isolated from leaves of *Abrus precatorius* L. *3 Biotech* 2018;8(8):1-4.
- 10. Li Y, Dong C, Xu MJ, Lin WH. New alkylated benzoquinones from mangrove plant *Aegiceras corniculatum* with anticancer activity. *J Asian Nat Prod Res* 2019;22(2), 121-30.
- 11. Bailly C. Anticancer properties and mechanism of action of the quassinoid ailanthone. *Phytother Res* 2020;34(9):2203-13.
- 12. Ahamed A, Panneerselvam A, Alaklabi A, Arif IA, Ambikapathy V, Thajuddin N. Molecular perspective and anticancer activity of medicinal plants. *Saudi J Biol Sci* 2020;27(2):666-75.
- 13. Wang CM, Yeh KL, Tsai SJ, Jhan YL, Chou CH. Anti-proliferative activity of triterpenoids and sterols isolated from *Alstonia scholaris* against non-small-cell lung carcinoma cells. *Molecules* 2017;22(12):2119.
- 14. Li L, Yue GG, Lee JK, Wong EC, Fung KP, Yu J, et al. The adjuvant value of *Andrographis paniculata* in metastatic esophageal cancer treatment—from preclinical perspectives. *Sci Rep* 2017;7(1):1-4.
- 15. Al-Sheddi ES, Al-Zaid NA, Al-Oqail MM, Al-Massarani SM, El-Gamal AA, Farshori NN. Evaluation of cytotoxicity, cell cycle arrest and apoptosis induced by *Anethum graveolens* L. essential oil in human hepatocellular carcinoma cell line. *Saudi Pharm J* 2019;27(7):1053-60.
- 16. Daddiouissa D, Amid A. Anticancer activity of acetogenins from *Annona muricata* fruit. *IMJM* 2018;17(3):103-12.
- 17. Sugier P, Jakubowicz-Gil J, Sugier D, Kowalski R, Gawlik-Dziki U, Kołodziej B, et al. Chemical characteristics and anticancer activity of essential oil from *Arnica montana* L. rhizomes and roots. *Molecules* 2020;25(6):1284.
- 18. Koyuncu, I. Evaluation of anticancer, antioxidant activity and phenolic compounds of *Artemisia absinthium* L. extract. *Cell Mol Biol* 2018;64(3):25-34.
- 19. Zhang F, Zhang YY, Sun YS, Ma RH, Thakur K, Zhang JG, et al. Asparanin A from *Asparagus officinalis* L. Induces G₀/G₁ Cell Cycle Arrest and Apoptosis in Human Endometrial Carcinoma Ishikawa Cells via Mitochondrial and PI3K/AKT Signaling Pathways. *J Agric Food Chem* 2020;68(1):213-24.
- 20. Sombatsri A, Thummanant Y, Sribuhom T, Wongphakham P, Senawong T, Yenjai C. Atalantums H-K from the peels of *Atalantia monophylla* and their cytotoxicity. *Nat Prod Res* 2020;34(15):2124-30.
- 21. Agrawal S, BablaniPopli D, Sircar K, Chowdhry A. A review of the anticancer activity of *Azadirachta indica* (Neem) in oral cancer. *J Oral Biol Craniofac Res* 2020;10(2):206-9.
- 22. Kumar SS, Manoj P, Giridhar P, Shrivastava R, Bharadwaj M. Fruit extracts of *Basella rubra* that are rich in bioactives and betalains exhibit antioxidant activity and cytotoxicity

against human cervical carcinoma cells. *J Funct Foods* 2015;15:509-15.

23. Deepika S, Selvaraj CI, Roopan SM. Screening bioactivities of *Caesalpinia pulcherrima* L. swartz and cytotoxicity of extract synthesized silver nanoparticles on HCT116 cell line. *Mater Sci Eng C Mater Biol Appl* 2020;106:110279.

24. Ahmed SI, Hayat MQ, Tahir M, Mansoor Q, Ismail M, Keck K, et al. Pharmacologically active flavonoids from the anticancer, antioxidant and antimicrobial extracts of *Cassia angustifolia* Vahl. *BMC Complement Altern Med* 2016;16(1):1-9.

25. Prabhu A, Krishnamoorthy M, Prasad DJ, Naik P. Anticancer activity of friedelin isolated from ethanolic leaf extract of *Cassia tora* on HeLa and HSC-1 cell lines. *Indian J Appl Res* 2011;3(10):1-4.

26. Sheikh S, Siddiqui S, Dhasmana A. *Cissus quadrangularis* Linn. Stem ethanolic extract liberates reactive oxygen species and induces mitochondria mediated apoptosis in KB cells. *Pharmacogn Mag* 2015;11(Suppl 3):S365.

27. Park HR, Lee HS, Cho SY, Kim YS, Shin KS. Anti-metastatic effect of polysaccharide isolated from *Colocasia esculenta* is exerted through immunostimulation. *Int J Mol Med* 2013;31(2):361-8.

28. Peng L, Hu C, Zhang C, Lu Y, Man S, Ma L. Anti-cancer activity of *Conyza blinii* saponin against cervical carcinoma through MAPK/TGF- β /Nrf2 signaling pathways. *J Ethnopharmacol* 2020;251:112503.

29. Rahman MA, Akhtar J. Evaluation of anticancer activity of *Cordia dichotoma* leaves against a human prostate carcinoma cell line, PC3. *J Tradit Complement Med* 2017;7(3):315-21.

30. Ege B, Yumrutas O, Ege M, Pehlivan M, Bozgeyik I. Pharmacological properties and therapeutic potential of saffron (*Crocus sativus* L.) in osteosarcoma. *J Pharm Pharmacol* 2020;72(1):56-67.

31. Kwon SB, Kim MJ, Yang JM, Lee HP, Hong JT, Jeong HS, et al. *Cudrania tricuspidata* stem extract induces apoptosis via the extrinsic pathway in SiHa cervical cancer cells. *PLoS One* 2016;11(3):e0150235.

32. Goodarzi S, Tabatabaei MJ, Mohammad Jafari R, Shemirani F, Tavakoli S, Mofasseri M, et al. *Cuminum cyminum* fruits as source of luteolin- 7-O-glucoside, potent cytotoxic flavonoid against breast cancer cell lines. *Nat Prod Res* 2020;34(11):1602-6.

33. Tuama AA, Mohammed AA. Phytochemical screening and *in vitro* antibacterial and anticancer activities of the aqueous extract of *Cucumis sativus*. *Saudi J. Biol Sci* 2019;26(3):600-4.

34. Shallan MA, Ali MA, Meshraf WA, Marrez DA. *In vitro* antimicrobial, antioxidant and anticancer activities of globe artichoke (*Cynara cardunculus* var. *scolymus* L.) bracts and receptacles ethanolic extract. *Biocatal Agri Biotechnol* 2020;29:101774.

35. Wang J, Wu M, Zheng D, Zhang H, Lv Y, Zhang L, et al. Garcinol inhibits esophageal cancer metastasis by suppressing the p300 and TGF- β 1 signaling pathways. *Acta Pharmacol Sin* 2020;41(1):82-92.

36. Zhou D, Jiang C, Fu C, Chang P, Yang B, Wu J, et al. Antiproliferative effect of 2-Hydroxy-6-tridecylbenzoic acid from *Ginkgo biloba* sarcotestas through the aryl hydrocarbon receptor pathway in triple-negative breast cancer cells. *Nat Prod Res* 2020;34(6):893-97.

37. Zhang B, Yan M, Zhang W, Ke ZY, Ma LG. *Glycyrrhiza glabra* suppresses nasopharyngeal carcinoma cell proliferation through inhibiting the expression of lncRNA, AK027294. *Biosci Biotechnol Biochem* 2020;84(2):314-20.

38. Kwak AW, Choi JS, Liu K, Lee MH, Jeon YJ, Cho SS, et al. Licochalcone C induces cell cycle G1 arrest and apoptosis in human esophageal squamous carcinoma cells by activation of the ROS/MAPK signaling pathway. *J Chemother* 2020;32(3):132-43.

39. Li T, Pan H, Feng Y, Li H, Zhao Y. Bioactivity-guided isolation of anticancer constituents from *Hedera nepalensis* K. Koch. *S Afr J Bot* 2015;100:87-93.

40. Shaikh R, Pund M, Dawane A, Iliyas S.

Evaluation of anticancer, antioxidant, and possible anti-inflammatory properties of selected medicinal plants used in Indian traditional medication. *J Tradit Complement Med* 2014;4(4):253-7.

41. Nair RVR, Jayasree DV, Biju PG, Baby S. Anti-inflammatory and anticancer activities of erythrodiol-3-acetate and 2,4-di-tert-butylphenol isolated from *Humboldtia unijuga*. *Nat Prod Res* 2020;34(16):2319-22.

42. Yan YY, Zhang Q, Zhang B, Yang B, Lin NM. Active ingredients of *Inula helenium* L. exhibits similar anti-cancer effects as isoalantolactone in pancreatic cancer cells. *Nat Prod Res* 2020;34(17):2539-44.

43. Mbaoji FN, Behnisch-Cornwell S, Ezike AC, Nworu CS, Bednarski PJ. Pharmacological Evaluation of the Anticancer Activity of Extracts and Fractions of *Lannea barteri* Oliv. (Anacardiaceae) on Adherent Human Cancer Cell Lines. *Molecules* 2020;25(4):849.

44. Goh MP, Kamaluddin AF, Tan TJ, Yasin H, Taha H, Jama A, Ahmad N. An evaluation of the phytochemical composition, antioxidant and cytotoxicity of the leaves of *Litsea elliptica* Blume—An ethnomedicinal plant from Brunei Darussalam. *Saudi J Biol Sci* 2022;29(1):304-17.

45. Al-Dabbagh B, Elhaty IA, Elhaw M, Murali C, Al Mansoori A, Awad B, et al. Antioxidant and anticancer activities of chamomile (*Matricaria recutita* L.). *BMC Res Notes* 2019;12(1):1-8.

46. Utari F, Efdi M, Ninomiya M, Tanaka K, Win KM, Nishina A, et al. N 2-Methylaurantiamide acetate: a new dipeptide from *Mimusops elengi* L. flowers. *Med Chem Res* 2019;28(5):797-803.

47. Khurshid Y, Syed B, Simjee SU, Beg O, Ahmed A. Antiproliferative and apoptotic effects of proteins from black seeds (*Nigella sativa*) on human breast MCF-7 cancer cell line. *BMC Complement Med Ther* 2020;20(1):1-11.

48. Jamali T, Kavoosi G, Ardestani SK. *In-vitro* and *in-vivo* anti-breast cancer activity of OEO (*Oliveria decumbens* vent essential oil) through promoting the apoptosis and immunomodulatory effects. *J Ethnopharmacol* 2020;248:112313.

49. Sokmen A, Abdel-Baki AA, Al-Malki ES, Al-Quraishi S, Abdel-Haleem HM. Constituents of essential oil of *Origanum minutiflorum* and its *in vitro* antioxidant, scolicidal and anticancer activities. *J King Saud Univ Sci* 2020;32(4):2377-82.

50. Baek SJ, Lee H, Park SM, Park M, Yi JM, Kim NS, et al. Identification of a novel anticancer mechanism of *Paeoniae Radix* extracts based on systematic transcriptome analysis. *Biomed Pharmacother* 2022;148:112748.

51. Hawthorne B, Lund K, Freggiaro S, Kaga R, Meng J. The mechanism of the cytotoxic effect of *Panax notoginseng* extracts on prostate cancer cells. *Biomed Pharmacother* 2022;149:112887.

52. Xia C, Chen L, Sun W, Yan R, Xia M, Wang Y, et al. Total saponins from *Paris forrestii* (Takht) H. Li. show the anticancer and RNA expression regulating effects on prostate cancer cells. *Biomed Pharmacother* 2020;121:109674.

53. Sahyon HA, Al-Harbi SA. Antimicrobial, anticancer and antioxidant activities of nano-heart of *Phoenix dactylifera* tree extract loaded chitosan nanoparticles: *In vitro* and *in vivo* study. *Int J Biol Macromol* 2020;160:1230-41.

54. Mohamed SI, Jantan I, Nafiah MA, Seyed MA, Chan KM. Lignans and Polyphenols of *Phyllanthus amarus* Schumach and Thonn Induce Apoptosis in HCT116 Human Colon Cancer Cells through Caspases-Dependent Pathway. *Curr Pharm Biotechnol* 2021;22(2):262-73.

55. Longato GB, Rizzo LY, de Oliveira Sousa IM, Tinti SV, Possenti A, Figueira GM, et al. *In vitro* and *in vivo* anticancer activity of extracts, fractions, and eupomatenoid-5 obtained from *Piper regnellii* leaves. *Planta Med* 2011;77(13):1482-8.

56. Gusson-Zanetoni JP, da Silva JS, Picão TB, Cardin LT, Prates J, Sousa SO, et al. Effect of *Piper cubeba* total extract and isolated lignans on head and neck cancer cell lines and normal fibroblasts. *J Pharmacol Sci* 2022;148(1):93-102.

57. Fadaeinab M, Karimian H, Omar H, Taha H, Khorasani A, Banisalam B, et al. Reflexin A, a new indole alkaloid from *Rauvolfia reflexa* induces apoptosis against colon cancer cells. *J Asian Nat Prod Res* 2020;22(5):474-88.

58. Mahomoodally MF, Sieniawska E, Sinan KI, Nancy Picot-Allain MC, Yerlikaya S, Cengiz Baloglu M, et al. Utilisation of *Rhododendron luteum* Sweet bioactive compounds as valuable source of enzymes inhibitors, antioxidant, and anticancer agents. *Food Chem Toxicol* 2020;135:111052.

59. Farooq M, Abutaha N, Mahboob S, Baabbad A, Almoutiri ND, Wadaan MAAM, et al. Investigating the antiangiogenic potential of *Rumex vesicarius* (humeidh), anticancer activity in cancer cell lines and assessment of developmental toxicity in zebrafish embryos. *Saudi J Biol Sci* 2020;27(2):611-22.

60. Maheshwari R, Shreedhara CS, Polu PR, Managuli RS, Xavier SK, Lobo R, et al. Characterization of the Phenolic Compound, Gallic Acid from *Sansevieria roxburghiana* Schult and Schult. f. Rhizomes and Antioxidant and Cytotoxic Activities Evaluation. *Pharmacogn Mag* 2017;13(Suppl 3):S693-9.

61. Castro DTH, Campos JF, Damião MJ, Torquato HF, Paredes-Gamero EJ, Carollo CA, et al. Ethanolic Extract of *Senna velutina* Roots: Chemical Composition, *In vitro* and *In vivo* Antitumor Effects, and B16F10-Nex2 Melanoma Cell Death Mechanisms. *Oxid Med Cell Longev* 2019;2019.

62. Al-Massarani SM, El Gamal AA, Alam P, Al-Sheddi ES, Al-Oqail MM, Farshori NN. Isolation, biological evaluation and validated HPTLC-quantification of the marker constituent of the edible Saudi plant *Sisymbrium irio* L. *Saudi Pharm J* 2017;25(5):750-59.

63. Barhoi D, Upadhyaya P, Barbhuiya SN, Giri A, Giri S. Extracts of *Tagetes erecta* exhibit potential cytotoxic and antitumor activity that could be employed as a promising therapeutic agent against cancer: A study involving *in vitro* and *in vivo* approach. *Phytomed Plus* 2022;2(1):100187.

64. Hafezi K, Hemmati AA, Abbaszadeh H, Valizadeh A, Makvandi M. Anticancer activity and molecular mechanisms of α -conidendrin, a polyphenolic compound present in *Taxus yunnanensis*, on human breast cancer cell lines. *Phytother Res* 2020;34(6):1397-1408.

65. Patra S, Panda PK, Naik PP, Panigrahi DP, Praharaj PP, Bhol CS, et al. *Terminalia bellirica* extract induces anticancer activity through modulation of apoptosis and autophagy in oral squamous cell carcinoma. *Food Chem Toxicol* 2020;136:111073.

66. Syed A, Benit N, Alyousef AA, Alqasim A, Arshad M. *In-vitro* antibacterial, antioxidant potentials and cytotoxic activity of the leaves of *Tridax procumbens*. *Saudi J Biol Sci* 2020;27(2):757-61.

67. Qian S, Tong S, Wu J, Tian L, Qi Z, Chen B, et al. Paris saponin VII extracted from *Trillium tschonoskii* induces autophagy and apoptosis in NSCLC cells. *J Ethnopharmacol* 2020;248:112304.

68. Liang L, Amin A, Cheung WY, Xu R, Yu R, Tang J, et al. Parameritannin A-2 from *Urceola huaitingii* enhances doxorubicin-induced mitochondria-dependent apoptosis by inhibiting the PI3K/Akt, ERK1/2 and p38 pathways in gastric cancer cells. *Chem Biol Interact* 2020;316:108924.

69. Tian S, Wang Z, Wu Z, Wei Y, Yang B, Lou S, et al. Valtrate from *Valeriana jatamansi Jones* induces apoptosis and inhibits migration of human breast cancer cells *in vitro*. *Nat Prod Res* 2020;34(18):2660-63.

70. Hasibuan PA, Harahap U, Sitorus P, Satria D. The anticancer activities of *Vernonia amygdalina* Delile. Leaves on 4T1 breast cancer cells through phosphoinositide 3-kinase (PI3K) pathway. *Heliyon* 2020;6(7):e04449.

71. Tuasha N, Escobar Z, Seifu D, Gadisa E, Petros B, Sterner O, et al. Cytotoxic and other bioactivities of a novel and known sesquiterpene lactones isolated from *Vernonia leopoldi* (Sch. Bip. ex Walp.)

Vatke in breast cancer cell lines. *Toxicol Rep* 2022;9:382-92.

72. Ahmad R, Fatima A, Srivastava AN, Khan MA. Evaluation of apoptotic activity of *Withania coagulans* methanolic extract against human breast cancer and Vero cell lines. *J Ayurveda Integr Med* 2017;8(3):177-83.

73. Chaudhary S, Devkar RA, Bhere D, Setty MM, Pai KS. Selective cytotoxicity and pro-apoptotic activity of stem bark of *Wrightia tinctoria* (Roxb.) R. Br. in cancerous cells. *Pharmacog. Mag* 2015;11(Suppl 3):S481.

74. Tian M, Liu T, Wu X, Hong Y, Liu X, Lin B, Zhou Y, et al. Chemical composition, antioxidant, antimicrobial and anticancer activities of the essential oil from the rhizomes of *Zingiber striolatum* Diels. *Nat Prod Res* 2020;34(18):2621-25.

75. Balasubramanian K, Padma PR. Anticancer activity of *Zea mays* leaf extracts on oxidative stress-induced Hep2 Cells. *J Acupunct Meridian stud* 2013;6(3):149-58.

76. Suvarna V, Bore B, Bhawar C, Mallya R. Complexation of phytochemicals with cyclodextrins and their derivatives-an update. *Biomed Pharmacother* 2022;149:112862.

77. Chen C, Wang J, Sun M, Li J, Wang HM. Toward the next-generation phyto-nanomedicines: Cell-derived nanovesicles (CDNs) for natural product delivery. *Biomed Pharmacother* 2022;145:112416.

78. Chaniad P, Phuwajaroanpong A, Techarang T, Viriyavejakul P, Chukaew A, Punsawad C. Antiplasmodial activity and cytotoxicity of plant extracts from the Asteraceae and Rubiaceae families. *Heliyon*. 2022;8(1):e08848.

79. Li Y, Zhang T, Korkaya H, Liu S, Lee HF, Newman B, et al. Sulforaphane, a dietary component of broccoli/broccoli sprouts, inhibits breast cancer stem cells. *Clin Cancer Res* 2010;16(9):2580-90.

80. RudolfE, Cervinka M. Sulforaphane induces cytotoxicity and lysosome- and mitochondria-dependent cell death in colon cancer cells with deleted p53. *Toxicol In Vitro* 2011;25(7):1302-09.

81. Xu C, Shen G, Chen C, Gélinas C, Kong AN. Suppression of NF-kappaB and NF-kappaB-regulated gene expression by sulforaphane and PEITC through IkappaBalpha, IKK pathway in human prostate cancer PC-3 cells. *Oncogene* 2005;24(28):4486-95.

82. Han K, Meng W, Zhang JJ, Zhou Y, Wang YL, Su Y, et al. Luteolin inhibited proliferation and induced apoptosis of prostate cancer cells through miR-301. *Onco Targets Ther* 2016;9:3085-94.

83. Wang W, Zhao FL, Zhang J, Gao DD. Luteolin induces apoptosis in mouse liver cancer cells through ROS mediated pathway: A mechanistic investigation. *Biomed Res* 2017;28(2):839-45.

84. Jeon YW, Ahn YE, Chung WS, Choi HJ, Suh YJ. Synergistic effect between celecoxib and luteolin is dependent on estrogen receptor in human breast cancer cells. *Tumor Biol* 2015;36(8):6349-59.

85. Dai J, Van Wie PG, Fai LY, Kim D, Wang L, Poyil P, et al. Downregulation of NEDD9 by apigenin suppresses migration, invasion, and metastasis of colorectal cancer cells. *Toxicol Appl Pharmacol* 2016;311:106-12.

86. Chunhua L, Donglan L, Xiuqiong F, Lihua Z, Qin F, Yawei L, et al. Apigenin up-regulates transgelin and inhibits invasion and migration of colorectal cancer through decreased phosphorylation of AKT. *J Nutr Biochem* 2013;24(10):1766-75.

87. Hassan ZK, Daghestani MH. Curcumin effect on MMPs and TIMPs genes in a breast cancer cell line. *Asian Pac J Cancer Prev* 2012;13(7):3259-64.

88. Zhou H, Beevers CS, Huang S. The targets of curcumin. *Curr Drug Targets* 2011;12(3):332-47.

89. Zhuang X, Dong A, Wang R, Shi A. Crocetin treatment inhibits proliferation of colon cancer cells through down-regulation of genes involved in the inflammation. *Saudi J Biol Sci* 2018;25(8):1767-71.

90. Samarghandian S, Borji A, Farahmand SK, Afshari R, Davoodi S. *Crocus sativus* L. (saffron) stigma aqueous extract induces apoptosis in alveolar human lung

cancer cells through caspase-dependent pathways activation. *Biomed Res Int* 2013;2013:417928.

91. Sorrenti V, Vanella L, Acquaviva R, Cardile V, Giofrè S, Di Giacomo C. Cyanidin induces apoptosis and differentiation in prostate cancer cells. *Int J Oncol* 2015;47(4):1303-10.

92. Cho E, Chung EY, Jang HY, Hong OY, Chae HS, Jeong YJ, et al. Anti-cancer Effect of Cyanidin-3-glucoside from Mulberry *via* Caspase-3 Cleavage and DNA Fragmentation *in vitro* and *in vivo*. *Anticancer Agents Med Chem* 2017;17(11):1519-25.

93. Mazewski C, Kim MS, Gonzalez de Mejia E. Anthocyanins, delphinidin-3-O-glucoside and cyanidin-3-O-glucoside, inhibit immune checkpoints in human colorectal cancer cells *in vitro* and *in silico*. *Sci Rep* 2019;9(1):11560.

94. Weller C, Horn S, Herrmann H. Photolysis of Fe (III) carboxylato complexes: Fe (II) quantum yields and reaction mechanisms. *J Photochem Photobiol A: Chem* 2013;268:24-36.

95. Kwak TW, Park SB, Kim HJ, Jeong YI, Kang DH. Anticancer activities of epigallocatechin-3-gallate against cholangiocarcinoma cells. *Onco Targets Ther* 2016;10:137-44.

96. Chen SJ, Yao XD, Peng BO, Xu YF, Wang GC, Huang J, et al. Epigallocatechin-3-gallate inhibits migration and invasion of human renal carcinoma cells by downregulating matrix metalloproteinase-2 and matrix metalloproteinase-9. *Exp Ther Med* 2016;11(4):1243-48.

97. Yeo C, Han DS, Lee HJ, Lee EO. Epigallocatechin-3-Gallate Suppresses Vasculogenic Mimicry through Inhibiting the Twist/VE-Cadherin/AKT Pathway in Human Prostate Cancer PC-3 Cells. *Int J Mol Sci* 2020;21(2):439.

98. Jia S, Xu X, Zhou S. Fisetin induces autophagy in pancreatic cancer cells *via* endoplasmic reticulum stress- and mitochondrial stress-dependent pathways. *Cell Death Dis* 2019;10(2):1-15.

99. Zhang XJ, Jia SS. Fisetin inhibits laryngeal carcinoma through regulation of AKT/NF-κB/mTOR and ERK1/2 signaling pathways. *Biomed Pharmacother* 2016;83:1164-74.

100. Hsieh MH, Tsai JP, Yang SF, Chiou HL, Lin CL, Hsieh YH, et al. Fisetin Suppresses the Proliferation and Metastasis of Renal Cell Carcinoma through Upregulation of MEK/ERK-Targeting CTSS and ADAM9. *Cells* 2019;8(9):948.

101. Zhou P, Wang C, Hu Z, Chen W, Qi W, Li A. Genistein induces apoptosis of colon cancer cells by reversal of epithelial-to-mesenchymal *via* a Notch1/NF-κB/slug/E-cadherin pathway. *BMC Cancer* 2017;17(1):813.

102. Sanaei M, Kavoosi F, Valiani A, Ghobadifar MA. Effect of Genistein on Apoptosis and Proliferation of Hepatocellular Carcinoma Hepa1-6 Cell Line. *Int J Prev Med* 2018;9:12.

103. Nasser MI, Zhu S, Hu H, Huang H, Guo M, Zhu P. Effects of imperatorin in the cardiovascular system and cancer. *Biomed Pharmacother* 2019;120:109401.