ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

RESURGENCE OF PHYTOMEDICINES: A PROMISING APPROACH FOR CANCER MANAGEMENT

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ARTICLE INFO

Key words:

Traditional Medicine; Cancer; Medicinal Plants; Phytomolecules; Phytochemicals; Phytoconstituents

Access this article online
Website: https://www.jgtps.com
Quick Response Code:

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 phytomoieties 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 sciences, Google scholars, 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. Major anticancer modes of action of these Phytomedicine were found to be due to the stimulation of apoptosis, cell cycle arrest, oxidative stress, and immune responses while inhibiting cellular proliferation, angiogenesis, and inflammation in cancer cells. 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 types of cancer that affect people worldwide include lung, breast, cervical, and prostate cancer. 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 derived 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 *In-vitro/In vivo* anticancer activity	Ref.
Abrus precatorius (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]
Aegiceras corniculatum (Aegiceratacеae)	Stems and twigs Petroleum ether	Benzoquinones, (2-hydroxy-5-ethoxy-3-nonyl-1,4-benzoquinone, 5-*O*-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-*O*-methylembelin, 5-*O*-methyl-rapanone, and 5-*O*-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]
Ailanthus altissima (Simaroubaceae)	Bark Dimethylsulfoxide	Ailanthone By inhibiting Hsp90 co- chaperone p23 and by modulating the expression of microRNAs	H-1975 (non-small cell lung cancer cell line), 22Rv1, LNCaP, VCap (castration-resistant prostate cancer cell lines), and xenograft mice bearing Huh7 (hepatocellular tumor cells)	[11]
Aloe castellorum (Asphodelaceae)	Leaf Methanolic	9-octadecenoic acid By inducing apoptosis	HCT116 (colorectal cancer cell line)	[12]

Aloe pseudorubroviolacea (Asphodelaceae)	Leaves Methanolic	3-dodecanol By inducing apoptosis	HCT116	[12]
Alstonia scholaris (Apocynaceae)	Leaf Hexane	Ursolic acid, betulinic acid, betulin, and 2β,3β,28-lup-20(29)-ene-triol By inhibiting proliferation	A549	[13]
Andrographis paniculata (Acanthaceae)	Aqueous Extract	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 cells) and metastatic esophageal xenograft-bearing mice	[14]
Anethum graveolens (Apiaceae)	Seed Essential oil	Carvone, dillapiole and dihydrocarvone By causing cell cycle arrest and inducing apoptosis	Hep G2	[15]
Annona muricate (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]
Arnica montana (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]
Artemisia absinthium (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]

Asparagus officinalis (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]
Atalantia monophyla (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]
Azadirachta indica (Meliaceae)	Leaf Ethanolic	Azadirachtin and Nimbolide By inducing apoptosis	KB, ORL 48, SCC131, SCC4, Cal27, HSC3 (oral cancer cell lines) and DMBA-induced tumor in hamster buccal pouch	[21]
Basella rubra (Basellaceae)	Fruit Aqueous and methanolic	Betalains, phenols, and flavonoids By inducing apoptosis	SiHa (cervical cancer cell line)	[22]
Caesalpinia pulcherrima (Fabaceae)	Leaf Petroleum ether, chloroform, ethyl acetate, and methanolic	Phenols and flavonoids By inducing apoptosis	HCT-116	[23]
Cassia angustifolia (Fabaceae)	Leaf Methanolic and ethanolic	Flavonoids like 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]
Cassia tora (Fabaceae)	Leaf Ethanolic	Friedelin By inducing apoptosis	HeLa and HSC-1(human skin cancer cell lines)	[25]
Cissus quadrangularis (Vitaceae)	Stem Ethanolic	Stigmast-4-en-3-one and octadecanoic acid By inducing apoptosis and upregulating p53 gene	KB	[26]
Colocasia esculenta (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]

Conyza blinii (Compositae)	Aerial parts Methanolic and Ethanolic	Triterpenoidal saponins By modulating MAPK/TGF-β/Nrf2 signaling pathways	HeLa and xenograft mice bearing HeLa	[28]
Cordia dichotoma (Boraginaceae)	Leaf Methanolic	Flavonoids By inducing apoptosis and scavenging free radicals	PC3	[29]
Crocus sativus (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]
Cudrania tricuspidata (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 *via* alteration of protein levels of p53 and p-pRb.	HPV-16-positive SiHa, CaSki (cervical cancer cells), and HaCaT (human normal keratinocytes)	[31]
Cuminum cyminum (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]
Curcumis sativus (Cucurbitaceae)	Leaf Methanolic and acetone extracts	Alkaloids, glycosides, steroids, saponins, and tannins By inducing apoptosis	MCF-7 and HeLa	[33]
Cynara cardunculus var. *scolymus* (Asteraceae)	Bract and receptacle Ethanolic	Phenols and flavonoids By causing cytotoxicity and scavenging free radicals in cancer cells	HepG2, MCF-7, and HCT-116	[34]

Dodonaea viscosa (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 in cancer cells	Brine shrimp lethality assay, HepG2, and THP-1 (human leukemia cell line)	[1]
Gambogic genera (Guttiferae)	Pericarp Dimethyl sulfoxide	Garcinol By suppressing p300 and TGF-β1 signaling pathways	KYSE150, KYSE450 (human oesophageal cancer cell lines) and pulmonary metastasis assay in BALC/c nude mice	[35]
Ginkgo biloba sarcotestas (GBS) (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]
Glycyrrhiza glabra (Fabaceae)	Root Aqueous	AK027294 By inhibiting the expression of lncRNA, and by inducing apoptosis	C666-1 (nasopharyngeal carcinoma cell line)	[37]
Glycyrrhiza inflata 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 cells (esophageal squamous cell carcinoma)	[38]
Hedera nepalensis (Araliaceae)	Leaves Ethanol extract	Hederagenin 3-O-α-L-arabinopyranoside and Pulsatilla saponin By inducing apoptosis	A549	[39]
Helicteres isora (Sterculiaceae)	Whole plant Hexane, ethanol and water	Flavonoids By inducing cytotoxicity	HeLa- B75, HL- 60, HEP- 3B, (human hepatoma cell line) and PN- 15 (renal cell carcinoma)	[40]
Humboldtia unijuga (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]
Inula helenium (Asteraceae)	Root Ethanol	Isoalantolactone, Alloalantolactone, and alantolactone	PANC-1 and SW1990 cells (pancreatic cancer cell lines)	[42]

		By inducing apoptosis		
Lannea barteri (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]
Lavandula bipinnata (Lamiaceae)	Whole plant Hexane, ethanol and water	Flavonoids By inducing cytotoxicity	HeLa- B75, HL- 60, HEP- 3B, PN- 15	[40]
Litsea elliptica (Lauraceae)	Leaves Methanolic and Ethanolic extract	Flavonoids, terpenes, alcohols, fatty acids and their methyl esters and vitamin E By inducing apoptosis	A549	[44]
Matricaria recutita (Asteraceae)	Flower Ethanolic	Phenols and flavonoids By inhibiting tumor angiogenesis and cell migration	HepG2	[45]
Mimusops elengi (Sapotaceae)	Flower Ethylacetate	N2-methyl aurantiamide (Dipeptide) By inducing apoptosis	HL-60	[46]
Nigella sativa (Ranunculaceae)	Seed	Proteins By inducing Apoptosis	MCF-7	[47]
Nauclea latifolia smith (Rubiaceae)	Stem bark Methanolic extract	Alkaloids, flavonoids, glycosides, saponins, tannins and coumarins By causing cytotoxicity	MCF-7, RD (Skeletal muscle cancer cell line)	[4]
Oliveria decumbens (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]
Origanum minutiflorum (Labiatae)	Leaf Essential oil	Carvacrol By inducing apoptosis	MCF-7, A549 and HepG2	[49]
Paeoniae Radix (Paeoniaceae)	Aqueous and Ethanolic	Oleanolic acid and Hederagenin By inhibiting Aurora kinase activity	A549	[50]
Panax notoginseng (Araliaceae)	Root Ethanol	Notoginsenoside and ginsenoside By decreasing the (Interleukin- 4) IL- 4 secretions, arresting the cell cycle at G2/M phase, and inducing	PCa (Prostate cancer) cells, LNCaP and 22Rv1 cells.	[51]

		the apoptosis.		
Paris forrestii (Melanthiaceae)	Rhizome Ethanolic and ethylacetate	PCT3 (total saponins from Paris forrestii) 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]
Phoenix dactylifera (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]
Phyllanthus amarus (Acanthaceae)	Ethanolic	Phyllanthin, hypophyllanthin, gallic acid, niranthin, greraniin, phyltetralin, isolintetralin, corilagin and ellagic acid *Via* induction of apoptosis	HCT116	[54]
Piper regnellii (Piperaceae)	Leaves Dichloromethane	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]
Piper cubeba (Piperaceae)	Hydroalcoholic extract	Lignans (cubebin, dihydrocubebin, ethylcubebin, hinokinin and methylcubebin) *Via* alteration in the expression of genes and proteins involved with inflammatory	Hep2 and SCC-25 (oral squamous carcinoma cells) and normal fibroblasts process	[56]
Pittosporum angustifolium Lodd. (Pittosporaceae)	Leaf, stamen and flower Aqueous methanolic	Chlorogenic acid, p-coumaric acid, caffeic acid, t-ferulic acid and rutin. By inducing cytotoxicity	HeLa and HT29 cells	[7]
Rauvolfia reflexa (Apocynaceae)	Bark Hexane and methanolic	Reflexin A, macusine B and vinorine By inducing apoptosis	HCT-116	[57]

Rhododendron luteum (Ericaceae)	Aerial parts Ethyl acetate, methanolic, and aqueous	Phenols and flavonoids By inhibiting proliferation and inducing cytotoxicity	A549	[58]
Rumex vesicarius (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]
Sansevieria roxburghiana (Asparagaceae)	Rhizome Ethyl acetate	Gallic acid By inhibiting proliferation and inducing cytotoxicity	HCT-116, HeLa, and MCF-7	[60]
Senna velutina (Fabaceae)	Root Ethanolic	catechin, anthraquinone, and piceatannol By inducing apoptosis and by causing cell cycle arrest	B16F10-Nex2 (Melanoma cell line) and subcutaneously injected B16F10-Nex2 in C57BL/6 mice	[61]
Sisymbrium irio (Brassicaceae)	Aerial parts n-Hexane	β-sitosterol, stigmasterol and β-sitosterol-β-d-glucoside By inducing cytotoxicity	MCF-7, HCT-116 and HepG2	[62]
Soymida fembrifuga (Miliaceae)	Whole plant Ethanol	Phenolic compounds By inducing cytotoxicity in cancer cells	HeLa- B75, HL- 60, HEP- 3B, and PN- 15	[40]
Tagetes erecta (Asteraceae)	Leaf aqueous extract	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 (laryngeal cancer cell line)	[63]
Taxus Yunnanensis (Taxaceae)	Wood Aqueous	α-Conidendrin By inducing apoptosis	MCF-7 and MDA-MB-231	[64]
Terminalia bellirica (Combretaceae)	Fruit	Gallic acid By scavenging free radicals and by inducing apoptosis	Cal33, SCC–25, SCC–4 (tongue squamous cell carcinoma), FaDu (pharynx squamous cell carcinoma), and Hep2	[65]
Tinospora cordifolia (Menispermaceae)	Whole plant Ethanol	Phenolic compounds By inducing cytotoxicity	HeLa- B75, HL- 60, HEP- 3B, PN- 15	[40]

Tridax procumbens Asteraceae	Leaf Methanolic, ethanolic, chloroform, and water	Alkaloids, carbohydrates, polyphenols, and tannins By inducing cytotoxicity	A549 and MCF-7	[66]
Trillium tschonoskii (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]
Urceola huaitingii (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]
Valeriana jatamansi (Valerianaceae)	Root and rhizome	Valtrate By inducing apoptosis and by causing cycle arrest at the G2/M stage	MCF-7, MDA-MB-231, and MCF-10A (human breast cancer cells)	[69]
Vernonia amygdalina (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-methylumbelliferonea nd, 4-methylumbelliferyl glucuronide Through Induction of apoptosis, enhanced cell accumulation on G2/M phases in the cell cycle, and inhibition of expression of PI3K and mTOR	4T1	[70]
*Vernonia leopoldi*Vatke (Asteraceae)	Leaf Ethyacetate	Sesquiterpene lactones (11ß,13-dihydrovernodalol, vernomenin, vernolepin, and 11ß,13-	MCF-7, MCF-10A and JIMT-1 (breast cancer cells)	[71]

		dihydrovernodalin) and flavonoids (apigenin, eriodyctiol, and luteolin) By inhibiting aldehyde dehydrogenase expressing cancer stem cell sub-population and TNF-α-induced translocation of NF-κB to the cell nucleus		
Withania coagulans (Solanaceae)	Fruit Methanolic	Withaferin A By inducing apoptosis	MDA-MB-231 and Vero (kidney cancer cell line)	[72]
*Wrightia tinctoria (*Apocynaceae)	Stem bark Petroleum ether and ethyl acetate	Lupeol and β-sitosterol By causing apoptosis	MCF-7 and HeLa	[73]
Zingiber striolatum (Zingiberaceae)	Rhizome Essential oil	β-phellandrene, sabinene, b-pinene, geranyl linalool, terpinen-4-ol, a-pinene, and crypton By causing cytoxicity	K562 (human leukemic cell line), A549, and PC-3	[74]
Zea mays (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-κB transcriptional activation and expression of VEGF (vascular endothelial growth factor), 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-κB, 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 MMP-9 (matrix metalloproteinase-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, NFNFκB, 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 control cell metastasis [87]. By interfering with several cellular signaling pathways, including nuclear factor (NF-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-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]. Cyanidin was isolated from mulberry-induced 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 cells), 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. EGCG shows anticancer activity by multiple mechanisms such as by acting as an antioxidant, inhibiting tumor cell proliferation, metastasis, angiogenesis, inhibiting nuclear factor-κB 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

Fisetina 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-κB/mTOR signaling pathways [99]. Fisetin was also found to suppress the growth and metastasis of RCC (renal cell carcinoma) *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 EMT (Epithelial-mesenchymal transition) *via* suppression of the Notch1/NF-κB/slug/E-cadherin pathway [101]. In another study, genistein was reported as a promising phytoconstituent against hepatocellular carcinoma cell line (Hepa 1-6) 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, mperatorin treatment increases the expression of (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 phytomoieties 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 Sciences, Google Scholars databases, and Scopus, 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 of manuscript & Overall supervision.

Acknowledgement: 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).

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