

Phytochemical Constituents of Medicinal Plants as Potential Anticancer Agents: A comprehensive review

Amjad Hussain (Corresponding Author)

Department of Eastern Medicine, University of Balochistan, Quetta, Pakistan

Email address. amjadkhattak333@gmail.com

Aadil Ameer Ali

Institute of Physiotherapy and Rehabilitation Sciences Shaheed Mohtarma Benazir Bhutto Medical University Larkana

Muhammad Arsalan

Faculty of Pharmacy, University of Balochistan, Quetta, Pakistan

Saif Ahmad

Department of Eastern Medicine, University of Balochistan, Quetta, Pakistan

Muhammad Zakaria

Department of Eastern Medicine, University of Balochistan, Quetta, Pakistan

Muhammad Qasim

Center For Advanced Studies In Vaccinology And Biotechnology (CASVAB)

Department of Eastern Medicine, University of Balochistan, Quetta, Pakistan

Sikandar Ishaq

Faculty of Biological Sciences, Department of Biotechnology University of Science and Technology Bannu, Khyber Pukhtoon Khwa, Pakistan

Muhammad Qasim

Khushal Khan Khattak University, District Karak, Pakistan

Wafa Zainab

Institute of Physiotherapy and Rehabilitation Sciences Shaheed Mohtarma Benazir Bhutto Medical University Larkana

Farred Khan

Center For Advanced Studies In Vaccinology And Biotechnology (CASVAB)

Gul Muhammad

Center For Advanced Studies In Vaccinology And Biotechnology (CASVAB)

ABSTRACT

Aim of the study: Medicinal plants play an important role in the treatment of various diseases. The use of interest of medicinal plants increases day by day. The aim of the current review is to collect the published data of medicinal plants having anticancer effects.

Methodology: Four search engines (Google scholar, Science direct, Scopus and PubMed) were searched from 01/01/2011- 01/01/2021 for anticancer activity of herbal medicines, anticancer medicinal plants, anticancer activity of alternative medicines, Antineoplastic activity of herbal medicines, anti-proliferative properties of medicinal plants and antitumor activity of herbal medicines. 365 research paper were searched in all the four search engine. 238 research paper were included while 127 research paper were excluded

from the study (Figure.1).

Conclusion: Medicinal plants contain phytochemical compounds (Alkaloids and phenols etc) which play an important role in the treatment of various types of cancer. The mechanism of various phytochemical compounds is the induction of apoptosis and arresting of cell cycle. The current review enlists the published data that medicinal plants possess potential effects against cancer.

Abbreviation: MPs (Medicinal plants), FTIR (Fourier-transform infrared spectroscopy), HPLC (High Performance Liquid Chromatography), TLC (Thin-layer chromatography), NMR (Nuclear magnetic resonance), DNA (Deoxyribonucleic acid) RNA (Ribonucleic acid), L (Leaves), B (Bark), F (Fruit).

Introduction

The word cancer is derived from Greek word “karkinos” which means crab. It is the abnormal growth of cells and second cause of death worldwide [1]. The incidence of cancer increases day by day. 19.3 million new cancer cases were estimated by International Agency for Research on Cancer in 2020. Moreover, the global burden of cancer is expected upto 28.4 million cases by 2040, which is 47% increased from 2020 [2].

The side effects of chemotherapeutic agents increase day by day. The interest of the people towards the use of medicinal plants increases because of least side effects. Evidence base studies through modern technique such as FTIR, HPLC, TLC, NMR etc explore that medicinal plants contain numerous amount of phytochemical compounds such as alkaloids, vitamins, carotenoids, terpenoids, terpinoids, isoterpinoids, flavonoids, isoflavonoids, phenols, polyphenols, tannins, glycosides, saponins, enzymes, minerals [3-5].

The National Cancer Institute gathered approximately 35,000 plant samples from 20 countries and tested approximately 114,000 extracts for anticancer activity. Over 3000 plant species have been reported to have antitumor properties. Cancer is one of the most common diseases in humans, and there is currently considerable scientific and commercial interest in the ongoing discovery of new anticancer agents from natural sources[6,7].

Approximately 60% of drugs have been derived from the natural sources are used to treat cancer. *Taxus diterpenes*, *Podophyllum lignans*, *vinca alkaloids*, and *Camptotheca alkaloids* are isolated from the medicinal plants having promising effects against various types of cancer. There are currently 16 new phytochemical compounds in clinical trials, 13 of which are in phase I or II while three are in phase III. Flavopiridol (*Dysoxylum binectariferum*) and meisoindigo (*Indigofera tinctoria*) were derived from medicinal plants having anticancer activity and possess less toxic effects as compared to conventional drugs. Herbal remedies are a popular alternative in cancer treatment in many countries around the world. Currently, more than 3000 species of plants in the world are believed to have anti-cancer properties. Globally, the prevalence of herbal products for cancer treatment is from 10-40%. Only in Europe, the expenditure on herbal anti-cancer products is estimated at around \$5 billion per year [8-12].

Bioactive natural compounds and their metabolites such as phenols, polyphenols, terpinoids flavonoids and alkaloids possess anticancer activity with various

mechanism of action. These phytochemical compounds have strong antioxidant activity which may lead to cause apoptosis or prevent proliferation of cancer cells [5,13-20].

Methodology

A comprehensive literature was searched in Google scholar, Science direct, Scopus and PubMed for the collection of data regarding medicinal plants having anticancer activity. The term anticancer medicinal plants (MPs), anticancer activity of herbal medicines, anticancer activity of alternative medicines, anticancer activity of complementary medicines, Anti-metastatic activity of MPs, Antineoplastic activity of herbal medicines (HM), anti-proliferative properties of MPs and antitumor activity of HMs were searched independently in databases from 2011-2021 and searched 365 research papers (RP) in all the four search engines. 103, 73, 90, 99 RP (Total 365) were searched in Google scholar, Science direct, Scopus and PubMed respectively. Research papers included from Google scholar were 68, Science direct 51, Scopus 57 and PubMed 62 (Total 238) while research papers excluded from Google scholar search were 35, Science direct 22, Scopus 33 and PubMed 37. The inclusion and exclusion criteria were based on relevancy and irrelevancy of the research papers to current study (Figure 1).

Research Paper Selection Flowchart

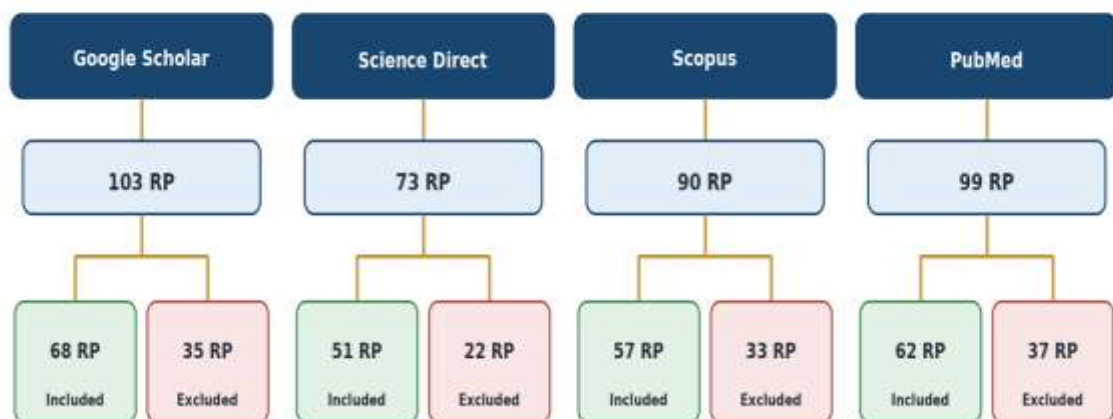


Figure 1. Methodology, RP (Research Paper)

Table 1: Anticancer effects of various medicinal Plants

BOTANICAL NAME/ Rf.no:	FAMILY	CHEMICAL CONSTITUENTS	PART USED	MECHANISM OF ACTION
<i>Ferula assa-foetida</i> (21-24)	Apiaceae	b-sitosterol, oleic acid, Coumarin compounds (especially sesquicoumarins), and sulfur-containing compounds.	Shoot, Resin	Increase of proteolytic enzymes activity; DNA destruction and cancer cells proliferation, Inhibition of mutagenesis.
<i>Thymus vulgaris</i> (25-27)	Lamiaceae	Carvacrol and Thymol.	Shoot	Cell cycle arrest
<i>Thymbra spicata</i> (28-30)	Lamiaceae	Carvacrol and Thymol.	Shoot	Inhibition of DNA destruction
<i>Taverniera sparteae</i> (31,32)	Leguminosae	Saponins and Isoflavonoid compounds.	Shoot	Induction of apoptosis and necrosis.
<i>Peganum harmala</i> (33-35)	Nitrariaceae	Alkaloids.	Seed	Increase proteolytic enzymes activity and causes apoptosis and activation of caspase
<i>Viola tricolor</i> (36-38)	Violaceae.	Flavonoids (rutin & quercetin)	Shoot	Cell cycle arrest and causes cell death
<i>Achillea wilhelmsii</i> (39-43)	Asteraceae	Phenolic compounds and monoterpenes e.g a-pinene and 1,8-cineole)	Shoot	Induction of apoptosis

<i>Mentha pulegium</i> (44-46)	Lamiaceae	isomenthone, menthone, piperitone, octen-3-ol, Pulegone, limonene.	Shoot	Induction of apoptosis
<i>Ammi visnaga</i> (47-50)	Apiaceae	kaempferol, Visnadine, quercetin, b-sitosterol, cimifugin, khellol.	Shoot	Cell cycle arrest
<i>Camellia sinensis</i> (20,51-55)	Theaceae	Epigallocatechin-3-gallate, Epicatechin, epigallocatechin epigallocatechin gallate...	Leaf	Inhibition of 5-a reductase enzyme and stop the proliferation of cancer cells.
<i>Avicennia marina</i> (56-58)	Acanthaceae	Naphthoquinone compounds like 3-chlorodeoxylapachol, these are Flavonoids compounds	Leaf	Antioxidant activity and initiation of program cell death.
<i>Silybum marianum</i> (59,60)	Asteraceae.	Silymarin	Seed	Antioxidant effects and cell cycle arrest
<i>Artemisia absinthium</i> (L) (61-64)	Asteraceae.	b-pinene, Artemisinin, myrcene, quercetin, limonene, a-pinene, isorhamnetin, artesunate, linalool.	Root, shoot	Induction of apoptosis, inhibition of angiogenesis and cell migration, cease cancer cells proliferation in response to nuclear receptors
<i>Curcuma longa</i> (65-72)	Zingiberaceae	Curcumin	Rhizome	inhibition of angiogenesis, Inhibition of cancer cells proliferation (by adjusting gene expression), induction of apoptosis.
<i>Crocus sativus</i> (L) (73-76)	Iridaceae	Phenolic compounds such as quercetin	Stigma	Inhibit DNA synthesis and stop the proliferation of cancer cells.

<i>Zingiber officinale</i> (66,77,78)	Zingiberaceae	Flavonoids (especially quercetin, kaempferol, fisetin, catechin)	Rhizome	Induction of apoptosis
<i>Olea europae</i> (52,79-81)	Oleaceae	acidic triterpenes, oleuropein, oleanolic acid, pinoresinol, maslinic acid, Oleic acid.	Leaf, fruit	inhibition of angiogenesis; Inhibition of cancer cells proliferation by inhibition of HER 2 gene expression, induction of apoptosis.
<i>Taxus baccata</i> (L) (82-84)	Taxaceae	Taxol	Leaf	Cell cycle arrest
<i>Nigella sativa</i> (85-90)	Ranunculaceae	Thymoquinone, dinitro quinone	Seed	induction of apoptosis; Cell cycle arrest.
<i>Allium sativum</i> (L) (91-101)	Amaryllidaceae	Ajoene, Allicin	Fruit	induction of apoptosis; Cell cycle arrest.
<i>Lepidium sativum</i> (102-104)	Brassicaceae	Glucosinolates, isothiocyanate, alpha linolenic acid and Vitamin A, B, C & E	Shoot	Cell cycle arrest; antioxidant effects.
<i>Trigonella foenum-graceum</i> (L) (105-108)	Fabaceae	Zingerone, cedrene, vanillin, eugenol, gingerol.	Shoot	Initiation of apoptosis and scavenging free radical effects
<i>Glycyrrhiza glabra</i> (109-112)	Fabaceae	Glycyrrhizin	Root	Inhibition of cancer cells proliferation (bcl-2 phosphorylation), Morphological variations in cancer cells and causes apoptosis.

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<i>Physalis alkekengi</i> (113-116)	Solanaceae.	Physalins	Fruit	Induction of apoptosis
<i>Lagenaria siceraria</i> Standl (117-121)	Cucurbitaceae	Saponins, Vitamin B&C, Cucurbitacin	Shoot, Fruit	Cell cycle arrest
<i>Ferula gummosa</i> (122-130)	Apiaceae	coumarins and Sesquiterpenes.	Shoot	Induction of apoptosis; Cell cycle arrest.
<i>Boswellia serrata</i> (131-133)	Burseraceae	Boswellic acid	Resin	Induction of apoptosis (by activation of caspases), decrease of cells viability by increasing the production of reactive oxygen species, Disturbance in synthesis of DNA, RNA and proteins and stop proliferation of cancer cells.
<i>Urtica dioica</i> (L) (134-138)	Urticaceae	Phenolic compounds	Leaf	Cell cycle arrest, Antioxidant effects.
<i>Ammi majus</i> (139-140)	Apiaceae	Coumarin compounds (especially psoralens)	Shoot, seed	induction of apoptosis; Cell cycle arrest
<i>Rosa damascene</i> (141-144)	Rosaceae	Phenolic compounds(epicatechin, catechin, gallic acid)	Petal	Antioxidant properties and protection of DNA.

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<i>Astragalus cystosus</i> (145-148)	Fabaceae	Terpenoids, Lectins, flavonoids	Shoot	induction of apoptosis; Cell cycle arrest
<i>Myrtus communis</i> (149-155)	Myrtaceae	Myrtucommulone, 1,8-cineole, limonene, α -terpinolene, Polyphenols, α -pinene, semi-myrtucommulone, myrtenol acetate, linalool.	Leaf	Induction of apoptosis (by activation of caspases) and Antioxidant effects
<i>Catharanthus roseus</i> (156-159)	Apocynaceae	vinflunine, Vincristine, catharanthine, vinblastine, vindoline.	Shoot	Effect microtubules and causes inhibition of cancer cells division/proliferation, Antioxidant activity
<i>Citrullus colocynthis</i> (160-164)	Cucurbitaceae	quercetin, Cucurbitacin, β -sitosterol.	Fruit	induction of apoptosis; Cell cycle arrest
<i>Polygonum aviculare</i> (165-168)	Polygonaceae	saponins, alkaloids, flavonoids, Tannins.	Shoot	Antioxidant effects; induction of apoptosis; cell cycle arrest
<i>Astroudaucus orientalis</i> (169-171)	Apiaceae	Fenchyl-acetate, myrcene, sabinene, α -copaene, α -pinene, α -thujene.	Root, shoot	induction of apoptosis; Cell cycle arrest
<i>Brassica</i> (172-174)	<u>Brassicaceae</u>	Sulphoraphane	Leaf	antiproliferate effects and inhibit growth of tumor in breast cancer.
<i>Papaver somniferum</i>	<u>Papaveraceae</u>	Noscapine	Seed	Inhibits tumor growth and progression, effects microtubule and cause cell death,

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				Antiproliferative activity
<i>Green tea</i> (<i>Camellia sinensis</i>)	Theaceae	Epigallacotechin-3-gallate	Leaf	Decrease DNA damage in oxidative stress, inhibit specific kinases, possess antioxidant activity, anti-proliferative Properties,; inhibit carcinogenesis induced by ultra violet rays or induced by chemically.
<i>Taxus brevifolia-L</i> (175-179)	<u>Taxaceae</u>	Paclitaxel (Taxol)	Leaf	Disruption of microtubule and spindle and block mitosis and causes cell death through apoptosis mechanism; it causes inhibition of translational machinery.
<i>Combretum caffrum</i>	Combretaceae	Combretastatin A-4 phosphate	Leaf	Anti-angiogenic; vasuclar shut-down of tumors; tumor necrosis
<i>Podophyllum peltatum-L</i> (180,181,178)	Berberidaceae	Epipodophyllotoxin	Leaf	Pro-apoptotic effects; cell cycle interference
<i>Raphanus sativus-L</i>	Brassicaceae	Roscovitine	Root	Inhibition of cyclin dependent kinases; reduction of cell cycle progression
<i>Catharanthus roseus</i> (175,178,181-183)	Apocynaceae	Vincristine, Vindesine, Vinblastine, Vinorelbine, Vinflunine	Flower, leaf	Anti-mitotic; microtubule inhibitor; bind to β -tubulin; microtubule

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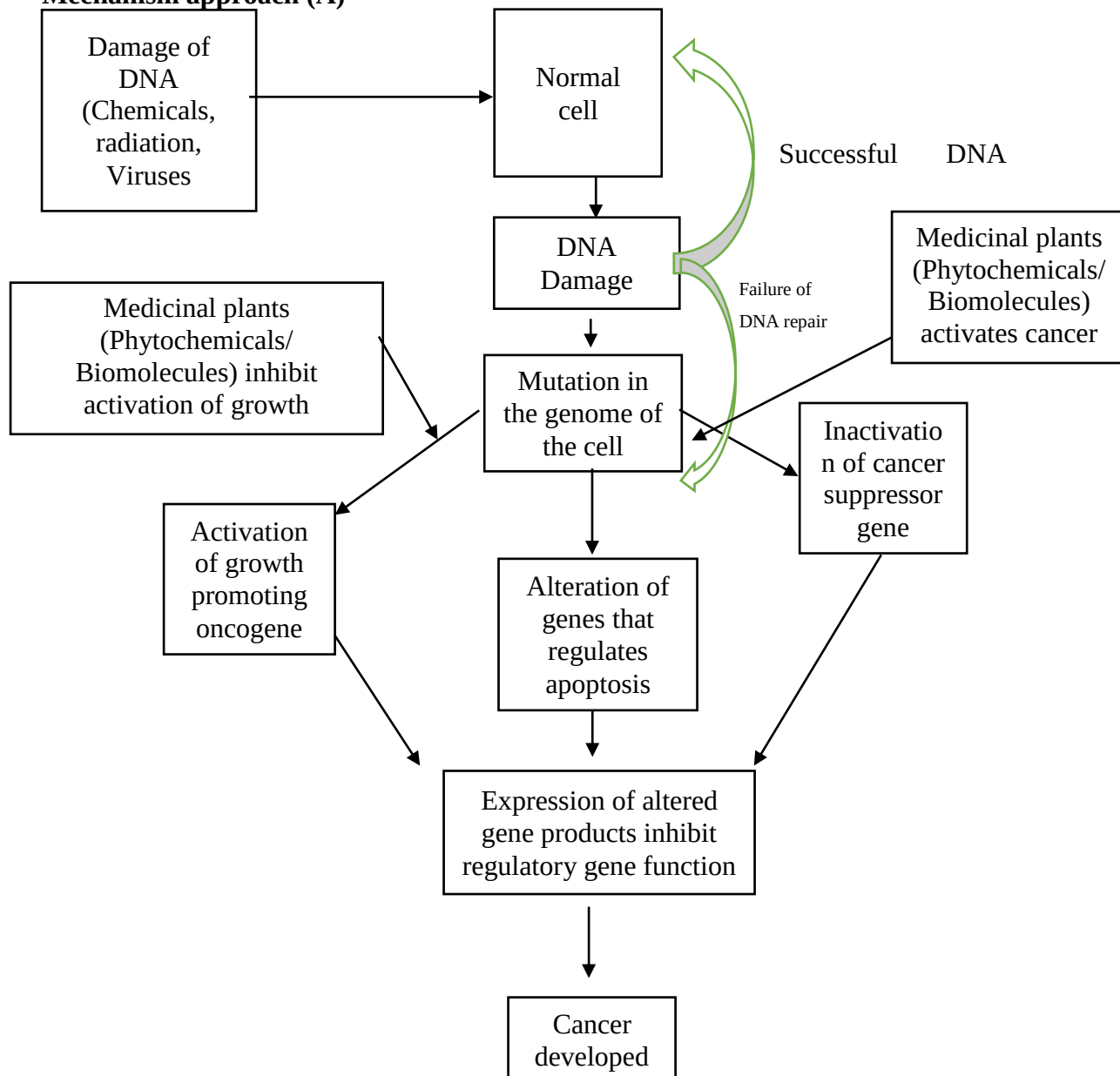
				stabilizers or destabilizers; pro-apoptotic properties and induce cell cycle arrest; anti-tumour activity
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Table 2. Some medicinal plants uses in various cancer

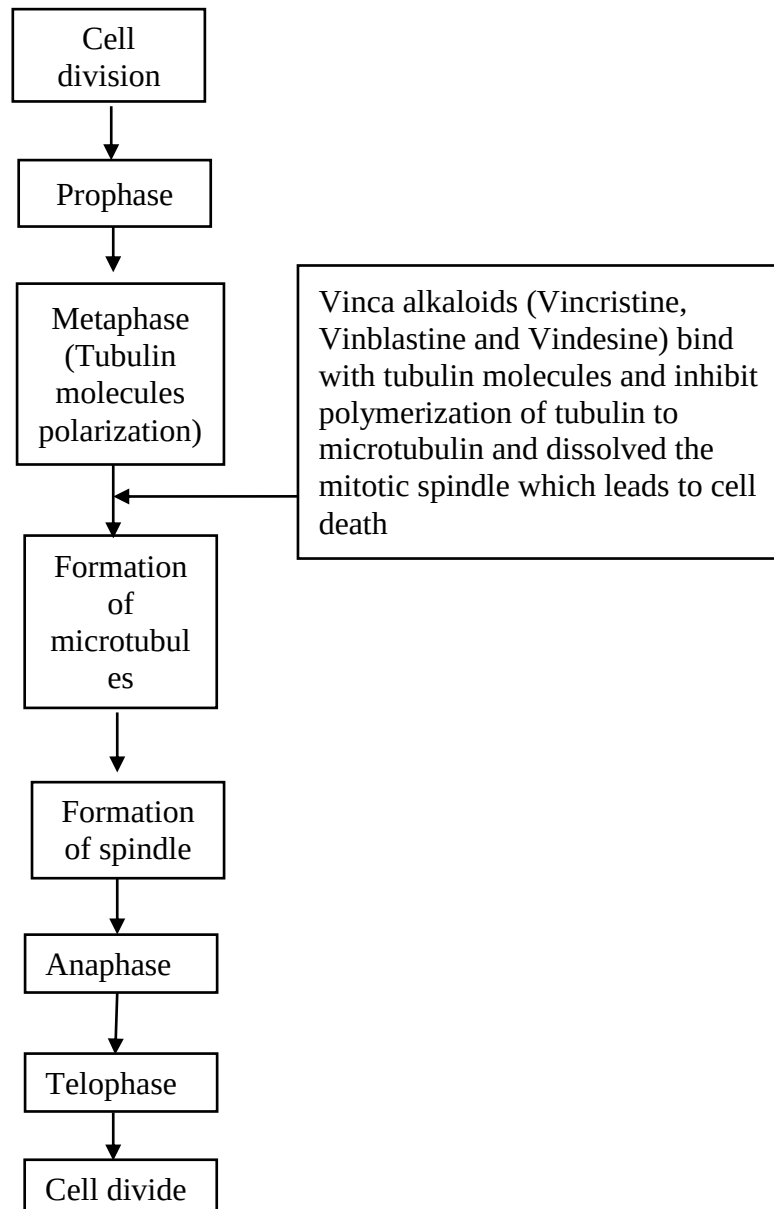
Botanical Name	Family	Part used	Type Of Cancer
<i>Beta vulgaris</i> (184,185)	Amaranthaceae	Leaves (L)	Blood cancer
<i>Allium sativum</i> L. (184)	Amaryllidaceae	Bulb (Blb)	Lungs cancer
<i>Daucus carota</i> L. (184, 187)	Apiace	Root (R)	Blood
<i>Opuntia species</i> (184, 193)	Cactace	L	Prostate, stomach, colon and rectum
<i>Euclea natalensis</i> A.DC. (193)	Caricaceae	Bark (B)	Prostate cancer
<i>Esculentus</i> (L.) Moench (184)	Malvaceae	Fruit (F)	Stomach, rectum and colon cancer
<i>Ficus dawei</i> (193)	Moraceae	B	Breast cancer
<i>Moringa oleifera</i> Lam (184, 193)	Moringaceae	L,B,R and Seed(Sd)	Prostate, lung, colon and rectal cancers
<i>Oxalis corniculata</i> L. (193)	Oxalidaceae	L	Skin and uterine cancer
<i>Prunus africana</i> (Hook.f.) (Pygeum africanum) (193)	Rosaceae	B,L	Prostate cancer
<i>Blighia unijugata</i> Baker (193)	Sapindaceae	B	Cervical cancer
<i>Zanthoxylum chalybeum</i> Engl. (193)	Rutaceae	R	Cervical cancer
<i>Capsicum frutescens</i> L. (193)	Solanaceae	F	Prostate cancer

Anticancer mechanistic approach of medicinal plants

Mechanism approach (A)



Mechanism approach (B)



Discussion:

Medicinal plants are being used from ancient time as natural healing substances having significant effects against various diseases. The plants contain various bioactive molecules having anticancer, anti-inflammatory, antioxidant, antimicrobial, antifungal, anticonvulsant, antibacterial activity. Additionally, the resistance of chemotherapeutic agents against various types of cancers has forced the researchers towards the alternative therapies for cancer. Medicinal plants have various bioactive natural products such as vinblastine, navelbine, vincristine and vindesine, Capillin (1-phenyl-2,4-pentadiyne) and Carvacrol etc have significant effects against cancer (194-200).

Conclusion

Medicinal plants are reservoir of numerous phytochemical substances. These phytochemical molecules have promising effects against various ailments. The major problems of chemotherapeutic agents are severe and prolong toxicity. However, plants derivative products/phytochemicals have least side effects as compared to the synthetic drugs. Many natural products and their metabolites have been isolated from the natural sources having potential effects against various types of cancers. Plant based anticancer molecules such as vinblastine, vincristine, topotecan, taxol, irinotecan, camptothecin derivatives and epipodophyllotoxins are used all over the world. The current review collects all the data of medicinal plants having chemotherapeutic properties and their mechanism of action. Further research work is required to identify the phytochemicals having anticancer activities and their structure elucidations as well as proper mechanism of action.

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