Review Paper:

Phytochemicals and their anticancer activity: An update on their mode of action

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Abstract

Many medicinal plants are well known in our country since time immemorial which reveal the invaluable knowledge of medicinal herbs to help in curing various diseases. Plants adapt to many physical and physiological defense mechanisms by production of secondary metabolites. The synergistic effects of herbal medicine contribute to greater potential in curing diseases compared to synthetic drugs. Role of research using herbs of medicinal importance is increasing rapidly during the preceding decade for development of new phytopharmaceuticals. Many new species of medicinal plants and their therapeutic effects were added to the already existing pharmacopeia. Modern medicine analyses biological effects of medicinal plants technically for novel drug development for accurate mode of action. This is an era where herbal medicine re-emerged as secondary metabolites showing numerous therapeutic effects focusing on identification, isolation and scale up of phytopharmaceuticals for manufacturing of drugs beneficial to humankind.

Various phytochemicals that play a role in anticancer properties along with mode of action are reviewed in present study. This review highlights the mechanism of antitumor action of some of the recent findings in plants focusing on regulating signaling pathways which paved the way in revolutionizing the pharma field. However, the study of medicinal plants should continue on unexplored plants without limitation. Mechanism of anticancer action of many explored and unexplored plants needs to be highlighted.

Keywords: Medicinal plants, secondary metabolites, phytochemicals, antimicrobial activity, mode of action.

Introduction

Phytochemicals and their derivatives have been identified as potential candidates for anticancer drug development due to their pleiotropic actions on target events with multiple manners. They have a promising role to improve efficiency of treatment in cancer patients by decreasing adverse reactions. Many phytochemicals are showing biological activity with significant antitumor potential. Dry and fresh plant materials are used for potential testing of biological activity in phytochemical based anticancer therapy. Active phytochemicals are purified and tested *in vitro* and *in vivo* as they are effective and free of side effects[15]. There are serious toxicity concerns to normal cells using numerous potent synthetic drugs causing obstacles in clinical utility over prolonged time duration.

Although numerous potent synthetic drugs have been introduced for cancer chemotherapy, yet their serious toxicity concerns to normal cells apart from drug resistance as the major obstacle for their clinical utility over a prolonged duration of time[46]. Several medicinal plant species and their phytochemicals inhibit the progression and development of cancer[8]. Phytochemicals and their derived analogues are present in different parts of the plant. Primary and secondary metabolites of plants were found to play significant role in either inhibiting cancer cell activating proteins, enzymes and signaling pathways. The efficacy of these Phyto molecules in cancer therapy is increased due to high biodegradability and biocompatibility[21]. Advancement of information technology and bioinformatics, increases the trend to build resources and databases on herbal formulations of active components and related information[25].

Role of plants in anti-cancer activity

After cardiovascular disease, cancer is the leading cause of death[27] as it is related with complex mechanisms both at cellular and molecular level. Phytochemical rich diet lessens cancer risk by 20%. These phytochemicals are generally natural plant derived secondary metabolites. Many challenges were faced during cancer treatment as patients undergo various types of therapies such as radiation, chemotherapy etc. Even then six million people die because of this disease worldwide every year.

It is recorded that there are about 22 million cancer patients in the world[39]. Anti-cancer agents avoid or repress the growth of cancer. Cancer is a serious disease caused by invasive growth of cells tending to proliferate rapidly causing malignancies in body. Cancer cells are formed as a result of imbalance in body metabolism and destroy healthy cells of our body. Cancer is treated by regulating body imbalance, thereby correcting abnormal behavior of cells. Imbalance in diet and hormones is the most important cause of cancer[3]. Cancer cells overlook the signals that normal cells take; thereby disturbing the process of programmed cell death (apoptosis).

Some natural plant sources acting as anti-tumor agents against various types of cancers in clinical use are vinblastine and vincristine from *Catharanthus roseus*, taxol from *Taxus brevifolia* Nutt., podophyllotoxin from *Podophyllum species* and homoharringtonine from *Cephalotaxus harringtonia*[24]. With the increasing concentration of *Phyllanthus amarus* leaf extract, the percentage viability of cancer cell lines was decreased[47]. Antimetastatic effects of four species of *Phyllanthus* namely *P. amarus, P. niruri, P. watsonii* and *P. urinaria* have been evaluated against human lung (A549) and breast cancer (MCF-7) cell lines and this plant has high anti-metastatic potential. It increases the level of caspase activity causing apoptosis induction.

Polyphenol compounds present in plant extracts of *P. amarus* were found to be responsible for anti-cancer activity[28]. It was reported that aqueous extract of *P. amarus* was found to inhibit aniline hydroxylase and DNA topoisomerase II enzymes in carcinogenic mice, which reduces tumor formation[43]. Lignan compounds namely phyllanthin, niranthin and nirtetralin of *P. amarus* also proved to cause anti-cancer effects[1]. Inhibition of cancer cell growth by cell cycle modulation and apoptosis induction using aqueous and methanolic extracts of four *Phyllanthus* species namely *P. amarus, P. niruri, P. watsonii and P. urinaria* were also investigated against prostate cancer and skin melanoma[51]. The compounds phyllanthin and hypophyllanthin of *P. amarus* proved to have cytotoxic activity[19].

Mechanisms of anti-cancer action: Many plants are reported to exhibit anticancer property since ancient times. Natural sources such as plants, micro-organisms and marine-organisms serve about 60% of the total anti-cancer agents[16]. Plants heal diseases like cancer without toxic side effects. It was proved that approximately 60% of cancer patients use medicinal herbs for effective cure of cancer[32]. The main causes behind the development of cancer such as chemical and biological agents, ionizing radiation, somatic mutations, reactive oxidative species were identified by WHO[50] as in fig. 1.

Roots of *Phyllanthus pulcher* Wall.ex Mull. Arg. were used for extraction of triterpenes compounds using dichloromethane, ethyl acetate and methanol solvents and these compounds were tested against breast, lung and prostate cancers[9]. Many medicinal plants play a major role as anticancer agents without causing any side effects. Medicinal plants such as *Podophyllum peltatum, Taxus brevifolia, Camptotheca acuminate, Cephalotaxus harringtonia, Catharanthus roseus* etc. have been reviewed and compounds such asbetulinic acid, combrestatin and silvesterol were found to be responsible for anticancer activity[24].

Methanolic extract of *Salacia oblonga* was evaluated for antiproliferative action against breast cancer. Compounds such as gammasitosterol, N-Methoxy-Nmethylacetamide, hexadecanoic acid, 12-dien-3-ol, Ursa-9(11) etc. have been identified through GC-MS analysis[6]. Different anticancer drugs have different mechanism of action and these mechanisms differ at various drug concentrations (Fig. 2). *P. amarus* in leaf extract revealed the presence of sylvatesmin which was reported to have high radical scavenging activity[48]. The aqueous extract of *Phyllanthus amarus* demonstrates potent anticancer activity against 20-metylcholanthrene (20-MC) induced sarcoma development. The aqueous extract inhibits DNA topoisomerase II of mutant cell cultures and inhibited cell cycle regulatory enzyme cdc 25 tyrosine phosphatase of *Saccharomyces cerevisiae*.

The anticarcinogenic and anti-tumour activity of *Phyllanthus amarus* proposed for inhibition of metabolic activation of carcinogen as well as for the inhibition of cell cycle regulators was responsible for cancerous growth and DNA repair[48]. Genistein reduces the risk of tumor formation and arrests invasion and angiogenesis by inhibiting protein tyrosine kinase and topoisomerase II. It also acts synergistically with other anticancer drugs. Genistein can also be used to supplement radiation treatment for prostate and breast carcinomas[5]. *In silico* docking analysis was done in *Phyllanthus amarus* plant for recognition of anticancer compounds viz. carissanol dimethyl ether, sylvatesmin, fumaric acid- 2-isopropylphenyl pentadecyl ester using AutoDock tools[47-49].

Plant derived bioactive compounds exert anticancer effects by the following mode of action[44]:

- Interferons induced cell death by blocking signaling pathway of growth factors.
- Cell death by DNA damage.
- Autophagy induction in response to starvation and stress by activation of tyrosine kinase and proteosome inhibitors.
- Induction of programmed cell death by use of glucocorticoid hormones in diseases such as lymphoblastic leukemia where the hormones affect glucose uptake by inhibiting glucose transporter expression.
- Disconnection of cellular metabolism from availability of nutrient and growth factors for limiting tumor cell growth as the metabolic demand is high.

Other mechanisms include[38]:

- Triggering apoptosis by inducing mutations in cancer cells.
- Interfering with DNA replication by use of alkylating agents.
- Cross linking in DNA strands inhibiting DNA, RNA and protein synthesis by use of heavy metals.
- Blocking of nucleic acid synthesis in cell cycle by use of antimetabolite compounds which compete with

natural substances such as vitamins, nucleosides or amino acids due to their structural similarity for receptors on essential enzymes.

- DNA fragmentation by using mixture of glycopeptides.
- Preventing reunion of DNA double helix during replication by stabilizing the DNA topoisomerase II complex using compounds such as anthracyclines.
- Preventing DNA replication by Topoisomerase inhibitors. This can be done by:
  - Topoisomerase I inhibitor which stabilizes the Topoisomerase I enzyme–DNA complex e.g. Camptothecin derived from *Camptotheca acuminata.*
  - Topoisomerase II inhibitors, which cause DNA strand breaks by stabilizing Topoisomerase II enzyme and DNA e.g. Epipodophyllotoxin derivatives of *Podophyllum peltatum.*
- Inhibiting mitotic spindle formation by blocking tubulin synthesis. This in turn influences DNA repair mechanism e.g. vincristine and vinblastine extracted from *Catheranthus roseus*, Taxol was derived from *Taxus brevifolia*.

There are numerous mechanisms for plant-derived anticancer drugs and most of them induce cell death by intrinsic or extrinsic apoptotic pathways, caspases or p53 dependent or independent mechanisms. Other methods include autophagy, senescence, necrosis and mitotic catastrophe causing cell death. Alkaloids, terpenoids and other secondary metabolite compounds of plant are found to exhibit anti-cancer properties[17]. As there is a problem of side effects with synthetic chemotherapeutic agents, plant derived compounds are gaining insight for exploiting novel pathways in cancer therapy. Cytotoxic compounds do not specifically target cancerous cells, but they influence ordinary cells also, showing adverse effects.

As plant based drugs have fewer side effects, research in plants is in continuous progress for isolating the active components for curing various types of cancers in an effective way. There should be more focus on target specific therapy and drug usage time for significant cure of cancers. Identifying the compounds which puts a check for malignant development is a hot topic in research at present (Fig. 3). Many medicinal plants possessing anti-cancer properties are listed in table 1.

Conclusion

Further studies on anticancer active ingredients (of plant origin) were encouraged using present study for their pharmacokinetic activities based on the fact that plant-based drug formulations generally consists of a number of phytochemicals from more than one plants. The major challenge would be to predict the role of phytochemicals other than active compounds that are present in the traditional medicines. Comprehensive analysis of different plants proved that medicinal herbs possess a huge anticancer potential. This review highlights the mechanism of antitumor action of some of the recent findings which focusses on regulating signaling pathways in plants.

Many studies have reported to stop tumor growth by inhibition of enzymes. It is highlighted that many plants play an important role in anticancer properties through their different classes of secondary metabolites (Table 1). However, the study of medicinal plants should still continue on various unexplored plants without limitation. Mechanism of anticancer action of many explored and unexplored plants needs to be highlighted

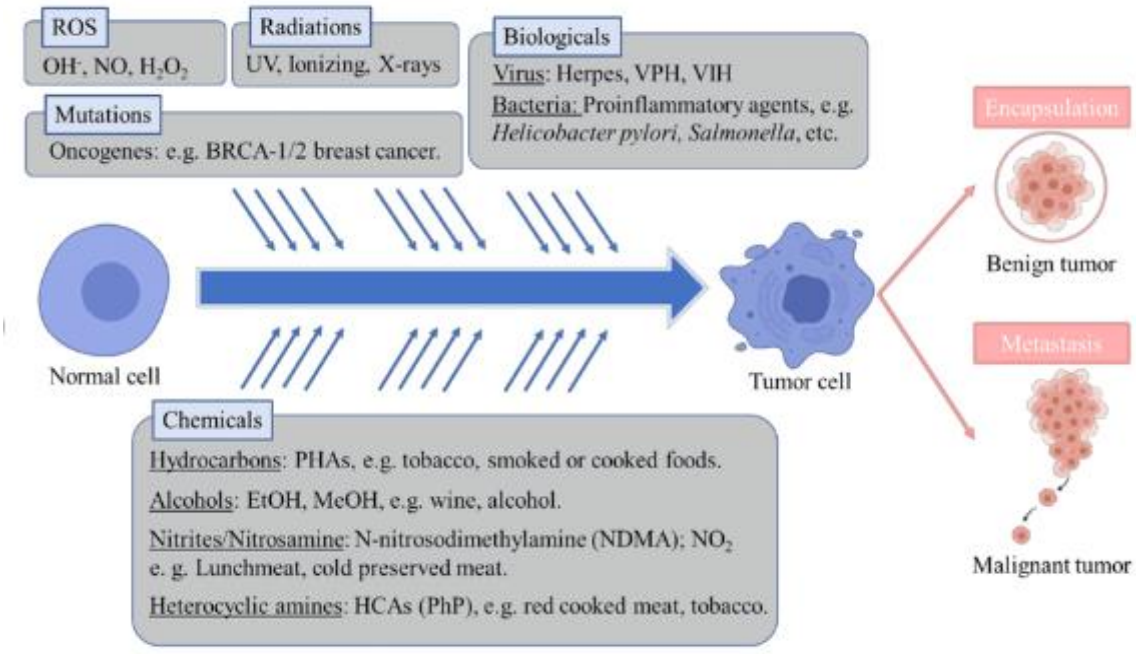

Fig. 1: Main causes involved in the development of cancer according to WHO.

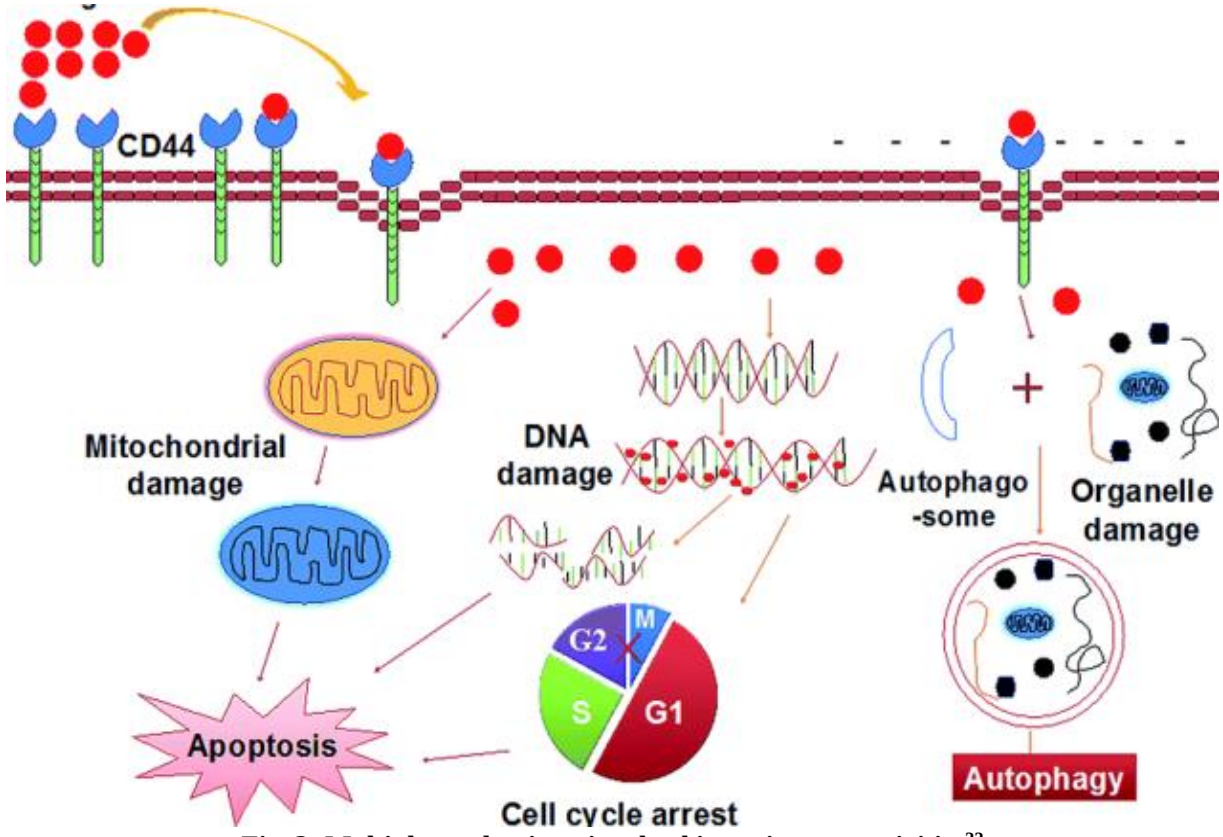

Fig. 2: Multiple mechanisms involved in anticancer activities[22]

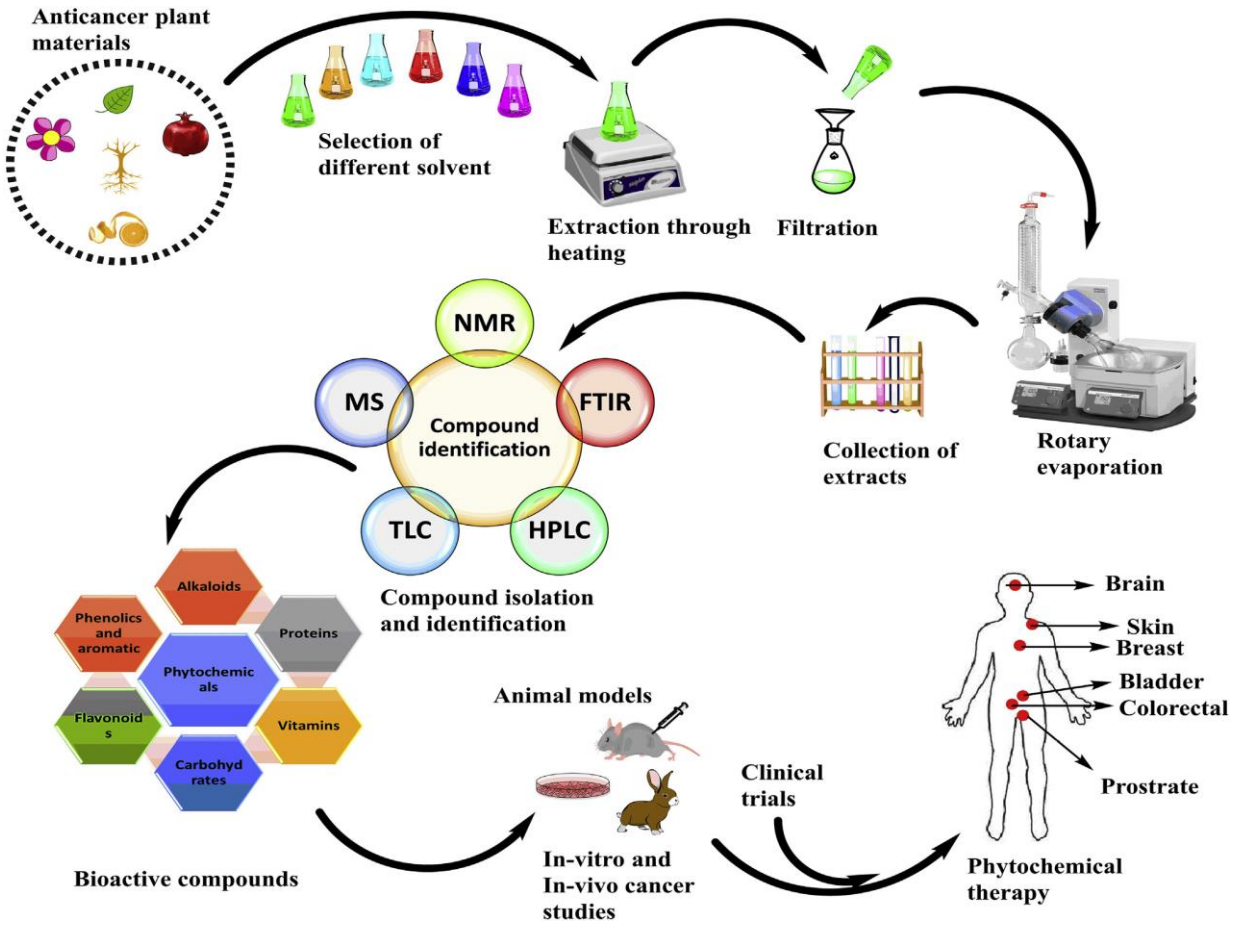

Fig. 3: Detailed scheme of anticancer phytochemical extraction, optimization, characterization and prospective use as cancer therapeutic agent[20]

Table 1
List of medicinal plants possessing anti-cancer properties

S.N.	Name of the plant	Family	Phytochemicals	Anti-cancer
1.	*Abelmoschus moschatus*[17]	Malvaceae	Phenols and Flavonoids.	Colorectal adenocarcinoma and retinoblastoma human cancer
2.	*Acacia pennivenia*[34]	Mimosaceae	Saponins and tannins.	Lung cancer, Urinary bladder Cancer and breast cancer.
3.	*Acanthospermum hispidum*[34]	Asteraceae	Sesquiterpene lactones	Lung cancer, urinary bladder cancer and breast cancer.
4.	*Acridocarpus socotranus*[34]	Malpighiaceae	Flavonoids, terpenoids.	Lung cancer, urinary bladder cancer and breast cancer.
5.	*Aloe perryi*[34]	Aloaceae	Anthraquinons, flavonoids.	Lung cancer, urinary bladder cancer and breast cancer.
6.	*Anthemis palestina*[10]	Asteraceae	Phenols and flavonoids. α-terpinene, β-terpinene, β-terpinolene, 1,8-cineole, menthone, isomenthone and citronellal, 1,8-cineole and terpinen-4-ol, thymol and carvacrol, eugenol.	Human breast adenocarcinom, human ductal breast epithelial tumor, Human colon adenocarcinoma, human epithelial carcinoma, human prostate adenocarcinoma, human clear cell renal cell carcinoma and human kidney carcinoma.
7.	*Ballochia atro-virgata*[34]	Acanthaceae	Terpenoids.	Lung cancer, urinary bladder cancer and breast cancer.
8.	*Bergenia ciliata*[2]	Saxifragaceae	Tannins, alkaloids, saponins, carbohydrates, flavonoids, steroids, phlobatannins, terpenoids, cardiac glycosides. Tannins, alkaloids, saponins, carbohydrates, flavonoids, steroids, phlobatannins, terpenoids, cardiac glycosides Tannins, alkaloids, saponins, carbohydrates, flavonoids, steroids, phlobatannins, terpenoids and cardiac glycosides.	Lung carcinoma and malignant melanoma
9.	*Blepharis spiculifolia*[34]	Acanthaceae	Phenolic compounds and terpenoids.	Lung cancer, urinary bladder cancer and breast cancer.
10.	*Boswellia dioscorides*[34]	Burseraceae	Volatile oil, terpenoids and flavonoids.	Lung cancer, urinary bladder cancer and breast cancer.
11.	*Boswellia socotrana*[34]	Burseraceae	Volatile oil, terpenoids and flavonoids.	Lung cancer, urinary bladder cancer and breast cancer.
12.	*Capparis cartilaginea*[34]	Capparaceae	Glucosinolates and flavonoids.	Lung cancer, urinary bladder cancer and breast cancer.
13.	*Cassia siamea*[23]	Fabaceae	Chromone (anhydrobarakol), Chromone alkaloids (barakol, cassiarin A-B), anthraquinones (chrysophanol, emodin), bianthraquinones (cassiamin A-B), flavonoids and phenolics.	Hepatic and mammary gland tumors, Human epidermoid carcinoma.
14.	*Commiphora ornifolia*[34]	Burseraceae	Volatile oil, terpenoids and flavonoids.	Lung cancer, urinary bladder cancer and breast cancer.

15.	*Corchorus erodioides*[34]	Tiliaceae	Flavonoids and phenolic compounds.	Lung cancer, urinary bladder cancer and breast cancer.
16.	*Crataegus monogyna L.*[37]	Rosaceae	Phenols and flavonoids.	Human skin fibroblasts and hepatocellular carcinoma.
17.	*Croton socotranus*[34]	Euphorbiaceae	Flavonoids, terpenoids and tannins.	Lung cancer, urinary bladder cancer and breast cancer.
18.	*Equisetum telmateia L.*[37]	Equisataceae	Phenols and flavonoids.	Human skin fibroblasts and hepatocellular carcinoma.
19.	*Euclea divinorum*[34]	Ebenaceae	Phenolic acids and tannins.	Lung cancer, urinary bladder cancer and breast cancer.
20.	*Euphorbia socotrana*[34]	Euphorbiaceae	Terpenoids, flavonoids, steroids and tannins.	Lung cancer, urinary bladder cancer and breast cancer.
21.	*Eureiandra balfourii*[34]	Cucurbitaceae	Terpenoids and flavonoids.	Lung cancer, urinary bladder cancer and breast cancer.
22.	*Ficus cordata*[34]	Moraceae	Tannins and terpenoids.	Lung cancer, urinary bladder cancer and breast cancer.
23.	*Ficus deltoidea*[28]	Moraceae	Phenol and 2, 4-bis (dimethylbenzyl)-6-t-butylphenol.	MTT assay against human breast adenocarcinoma.
24.	*Garcinia cowa*[45]	*Clusiaceae*	flavonoids, phloroglucinols, Xanthones and triterpene.	Hepatoma.
25.	*Geranium purpureum Vil.*[37]	Geraniaceae	Phenols and flavonoids. Phenols and flavonoids.	Human skin fibroblasts and hepatocellular carcinoma.
26.	*Glossonema revoili*[34]	Asclepiadaceae	Steroids and flavonoids.	Lung cancer, urinary bladder cancer and breast cancer.
27.	*Helicteres isora*[11,26]	Sterculiaceae	49-O-b -D-glucopyranosyl rosmarinic acid, 4,49-O-di-b -D-glucopyranosyl rosmarinic acid and 2R-O-(49-O-b -D-glucopyranosyl caffeoyl)-3-(4-hydroxyphenyl), lactic acid named as 49-O-b –D gluco pyranosyl isorinic acid and Rosmarinic acid.	oral carcinoma
28.	*Hibiscus noli-tangere*[34]	Malvaceae	Tannins and lignans.	Lung cancer, urinary bladder cancer and breast cancer.
29.	*Hypoestes pubescens*[34]	Acanthaceae	Alkaloids and terpenoids.	Lung cancer, urinary bladder cancer and breast cancer.
30.	*Lannea transulta*[34]	Anacardiaceae	Tannins and flavonoids.	Lung cancer, urinary bladder cancer and breast cancer.
31.	*Lavandula stoechas L. spp. luisieri*[34]	Lamiaceae	Phenols and flavonoids.	Human skin fibroblasts and hepatocellular carcinoma.
32.	*Leucas samhaensis*[34]	Labiatae	Volatile oil, terpenoids and flavonoids.	Lung cancer, urinary bladder cancer and breast cancer.
33.	*Leucas virgata*[34]	Labiatae	Volatile oil, terpenoids and flavonoids.	Lung cancer, urinary bladder cancer and breast cancer.
34.	*Limnophila aromatica*[18]	Scrophulariaceae	Eugenol, γ-terpinene.	--------
35.	*Lycium sokotranum*[34]	Solanaceae	Alkaloids.	Lung cancer, urinary bladder cancer and breast cancer.
36.	*Maerua angolensis*[34]	Capparaceae	Glucosinolates and tannins.	Lung cancer, urinary bladder cancer and breast cancer.
37.	*Melissa officinalis*[13]	Lamiaceae	Phenols.	Human epithelial cervical cancer and breast cancer.
38.	*Mentha suaveolens Ehrh.*[37]	Lamiaceae	Phenols and Flavonoids.	Human skin fibroblasts and hepatocellular carcinoma.
39.	*Michelia champaca*[28]	Magnoliaceae	Alkaloids, saponins, tannins, sterols, flavonoids and triterpenoids.	Colorimetric MTT (tetrazolium) assay against

				human breast adenocarcinoma.
40.	*Peperomia pellucida*[28]	Piperaceae	Phytol, 2-Naphtalenol, decahydro, Hexadecanoic acid, methyl ester ,9,12-Octadecadienoic acid(Z,Z)- and Methyl ester.	MTT (tetrazolium) assay against human breast adenocarcinoma
41.	*Polygonum odoratum*[35,41]	*Asparagaceae*	homoisoflavanones, isoflavones, flavone glycoside, triterpenoid aglycon, steroidal sapogenins, steroidal saponins, lignanoids and fatty acids.	Breast cancer carcinoma.
42.	*Psidium guajava*[12]	Myrtaceae	Tannins, flavonoids (myricetin, quercetin, luteolin and kaempferol), essential oils (caryophyllene, nerolidiol, β-bisabolene, aromadendrene, p-selinene, α-pinene and 1,8-cineol), triterpenoids (oleanic acid, ursolic acid, catecolic acid, guayavolic acid, maslinic acid, ellagic acid) and β-sitosterol.	Squamous cell carcinoma, meningioma cells, colon cancer.
43.	*Rhus thyrsiflora*[34]	Anacardiaceae	Flavonoids, terpenoids and tannins.	Lung cancer, urinary bladder cancer and breast cancer.
44.	*Ruta graveolens*[70]	Rutaceae	Furanocumarins, carotenoids, furanoquionolones.	MTT assay against breast cancer cell line
45.	*Strychnos lucida*[47]	Loganiaceae	Brucine, brucine N-Oxide, loganic acid, loganin, ligustrinoside, chlorogenic acid, 3,4-di-O-caffeoylquinic acid, β-D-glucoside, syringaresinol 4-O-βpicconioside I, sylvestroside I, vanillic acid 4-O- adenosine and 4-O-(3,5-dimethoxy-4-hydroxybenzoyl) quinic acid.	Hepatocellular carcinoma, cholangio carcinoma, lung carcinoma and T-lymphoblast, acute lymphoblastic leukemia cell lines.
46.	*Swertia chirata*[36]	Gentianaceae	Phenols and Flavonoids.	Human epidermoid *carcinoma*
47.	*Syzygium caryophyllatum (l)*[4,42]	Myrtaceae	Flavonoids, phenolic compounds, alkaloids and saponins.	Human liver carcinoma
48.	*Teucrium sokotranum*[34]	Labiatae	Volatile oil and terpenoids.	Lung cancer, urinary bladder cancer and breast cancer.
49.	*Tiliacora acuminata*[14]	Menispermaceae	Phenols and Flavonoids. alpha.-Tocopherol-beta.-D-mannoside, n-Hexatriacontane and Neophytadiene.	Human laryngeal carcinoma.

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