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Combinations of Plant Extracts and Drugs for Synergistic Anti –Cancer Activity- A Review

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Abstract

There has been an alarming growth of cancer patients in the world and the difficulties in the treatment of this disease have prompted the search for alternative strategies of treatment. Plant based treatments are not new, however, the effectiveness of these treatments need to be increased. In this regard, the synergistic effects can be advantageously exploited to obtain the best outcomes from natural plants. The multiple mechanisms of actions of different components in plant extracts can provide combinations with better efficacy and low doses. This method of screening involves the study of combinations of plant extracts with already reported activity or novel extracts. This review summarizes the various plant extract combinations which have been studied for their anti-cancer potential in order to estimate the current status on the synergistic effects of combinations of plant extracts with a focus on anticancer activity.

Keywords: Anti-cancer, synergistic, plant extract, combinations

INTRODUCTION

Morbidity and mortality rates are very high because of cancer. Cancer is a global health problem and serious health care issues for the human race.[1, 8] It needs to be controlled and demands a proactive strategy for cure. Although many types of cancer treatments are available such as surgery, radiotherapy, and chemotherapy but the treatments are accompanied by certain unbearable side effects. Cancer cells produce resistance to chemotherapeutic agents because of low selectivity of these agents against normal cells. Due to such resistance therapeutic dose may be increased and combination therapy using multiple drugs is used to achieve maximum efficacy and potency, with reduced toxicity in the treatment of cancer. [3]

Plants are reservoirs for novel chemical entities and provide a promising line for research on cancer. It has recently been argued that "the use of natural products has been the single most successful strategy in the discovery of novel medicines". Literature has also revealed that plant extracts have been used to treat various diseases and physical ailments including cancer. Most of the biological activities of traditionally used plant extracts have been shown to mediate through secondary metabolites synthesized by plants. [2] Owing to the fact that about 60% of clinically approved and marketed anti-cancer drugs are derived from plants, a large number of plants and their extracts have been screened for secondary metabolites responsible for therapeutic activity. [12] Previous researches have shown that herbal medicines derived from natural materials have lower side effects than modern medicine and provides important clues for identifying and developing combination/synergistic drugs. Carcinogenesis is a complex phenomenon where phytochemicals provide the anti-cancer action at multiple sites.There is increasing evidence for the potential of plant-derived compounds as inhibitors of various stages of carcinogenesis and associated inflammatory processes, underlining the importance of these products in cancer prevention and therapy.[1] Herbal mixtures containing a combination of different plant species have better biological activities than isolated active compounds and herbal mixtures prepared from one plant species. Therefore, these could be used to overcome the challenge of drug resistance. [13]

Through this review an effort has been made to highlight the plant extract combinations which exhibit synergistic anti-cancer activities. Furthermore, this review also discusses the synergistic effects observed when the plant extracts are given with anti-cancer agents (Table 1).

Synergistic effect of various plant extracts in cancer treatment

This section deals with the discussion of various plant extract combinations which have shown effective in vitro and in vivo anti-cancer activity and can provide effective therapeutic potential.

1)*Curcuma longa* and *Tinospora cordifolia* in cervical cancer

***Curcuma longa* (Turmeric)**

***Tinospora cordifolia*(Giloy)**

In women, cervical cancer is a major cause of mortality and morbidity. The main cause of cervical cancer is persistent viral infection by Human Papilloma Virus (HPV). Bacterial vaginitis, Herpes simplex virus 2, Chlamydia trachomatis or Trichomatis vaginalis all these infection act as cofactor for cervical cancer.

SRB (sulforhodamine B) assay was used for the evaluation of n-hexane extract of *Tinospora cordifolia* and ethanolic extract of *Curcuma longa*for cytotoxicity on C33a and SiHa cancer cell lines in which DMSO solvent used as control and podophyllotoxin used as positive control. Four concentrations of all compounds were prepared i.e. 25, 50, 100 and 200 µg/mlalong with the two mixtures of compounds containing 25 and 50 µg/ml of each extract. Both C33a and SiHa cancer cells were treated against these concentrations.

At higher concentration individual extract of *Curcuma* and *Tinospora* showed activity and took a longer period of time to produce activity, but did not show any effect on DNA. In addition, the mixture of two plant extracts act as potent anti-proliferative compounds. The mixture of plant extracts showed apoptosis in cancer cells and induced cell cycle arrest at G2M phase and cause DNA damagewhich could not be repaired and death of cancer cells occurred. [1]

2) *Rhizoma Corydalis and Rhizoma Curcumae* in breast cancer

Corydalis yanhusuo

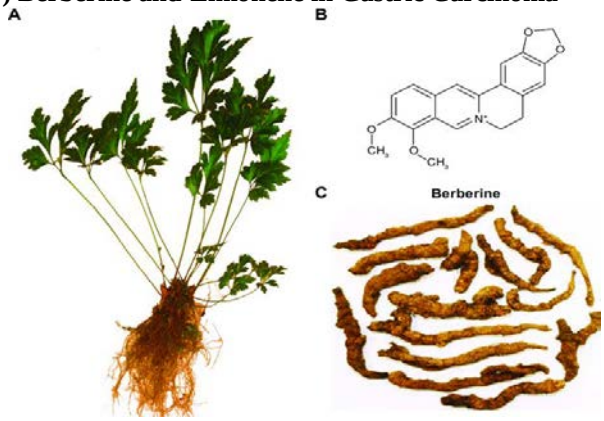
Curcuma wenyujin

Alcoholic extract of *Corydalis yanhusuo* and *Curcuma wenyujin* have been used individually and in combination for the anticancer activity. Both these extracts were evaluated by MTT assay on MDA-MB-231 breast cancer cells. Both extracts inhibited and suppressed the growth of MDA-MB-231 breast cancer cells in dose dependent manner. Anti-proliferative activity produced by cell apoptosis. The growth inhibition of cancer cells occurred due to cell cycle arrest, poly-ADP-ribose polymerase (PARP) degradation and loss of mitochondrial membrane potential, cytochrome c translocation, caspase 3 activation etc.

Individually extract showed 50% inhibition at higher dose butwhen theseextracts combined in 2:3ratio then at lower dose, shows strongest synergistic effect (CI- 0.7422)

In this method, if CI>1 it indicates antagonism, if CI=1 it showed additive effect, but if CI<1 it produced synergistic effect. [2]

3) Berberine and-Limonene in Gastric Carcinoma



Coptidis rhizome (Berberine)

Evodia rutaecarpa (d-Limonene)

Berberine is a component of *Coptidis rhizome* and d-Limonene is a component of *Evodia rutaecarpa*. The combined extracts exhibited antitumor effects on rat subjects.

The growth inhibitory effect of these components was determined by MTT assay on MGC803 gastric cancer cells. Chou- Talalay method was used for the calculation of combination index and drug reduction index which is based on median effect principle.Individually berberine and d-limonene inhibited the growth of cancer cell MGC803 in dose and time dependent manner. 1:4 combination ratio of berberine and d-limonene (20µM + 80µM) produced synergistic effect on gastric cancer cells by cell cycle arrest, intracellular ROS production and cell apoptosis through the mitochondria-mediated intrinsic

pathway. These two drugs reduced mitochondrial membrane potential (DCm) and decreased the expression of Bcl-2. When compared with cisplatin, the combination of these components showed more remarkable antiproliferative activity then cisplatin individually in MGC803 gastric cancer cells. [3]

4) *Descurainiae Sophia and Peucedani praeruptorum* in colon cancer

Descurainiae Sophia

Peucedani praeruptorum

BP10A is a novel two-herb medicine formula, consisting of *Descurainiae sophia* Semen and *Peucedani praeruptorum* Radix. Another name of *D. Sophia* is flixweed. In China and India, it is used to treat cough, fever, asthma and cardiac disease. Flixweed is found world-wide and its seeds are warm and wet in nature.

BP10A prepared by mixing ethanolic extract of *Descurainiae Sophia* and *Peucedani praeruptorum* mixed in 1:1 (w/w) ratio. Anti-cancer activity of BP10A was measured be Ez-Cytoxassay in two different human colorectal carcinoma cells, HCT-116 and KM12SM. Both cancer cells were treated with serial concentration of BP10A (0-200 µg/ml) for 48 hrs, BP10A produced cytotoxic activity in HCT-116 and KM12SM cancer cells in dose dependent manner and 16.78 and 42.39 µg/ml respectively was the EC50 i.e. half maximal effective concentration. Anticancer activity of BP10A due to degradation of poly ADP ribose polymerase (PARP). Viability of colorectal cancer cells were inhibited because of cell apoptosis exhibited by BP10A.[4]

5) *Zizuphus jujube* and *Camellia sinensis* in hepatic cancer

Zizyphus Jujuba

***Camellia sinensis* (Green tea leaves)**

In China, people drink *jujube* tea (*Z. jujuba* and green tea) for their better health. The chloroform extract of *Z. jujuba* showed anticancer activity on HepG2 liver cancer cells. When green tea extract used in combination with chloroform extract of *Z. jujube*, tea extract increased the cyotoxic activity of *jujube* extract in HepG2 cancer cells and inhibited the growth of cancer cells on G1 phase but did not show effect on apoptosis. It increased p53 and p21 proteins. When p21 increased then it binds with Cdk21 and inhibited its binding to cyclin E, which result in G1 phase arrest. According to authors G1 phase also restricted when the level of cyclin E decreased, resulting decrease in cyclin E-cdk2 complex.[5]

6) Curcumin and Resveratrol in various cancers

Curcuma longa

Polygonum cuspdatum

Rheum officinale

Resveratrol found in many plants like *Rheum officinale* Baill and *Polygonum cuspdatum*. It is natural phenol, mainly found in skin of grapes and red wine. Resveratrol used in traditional Chinese medicine from longerperiod of time.

Turmeric is obtained from rhizome of *Curcuma longa*, Indian plant belongs to Zingiberaceae family. Turmeric used in various food preparations. Curcumin used in prostate cancer, breast, colon and liver cancer because curcumin induced apoptosis in cancer cells and it inhibits proliferation of cells. Human-clinical trials showed curcumin safety, tolerability and nontoxicity at a high dose i.e. 8 g/day. Its therapeutic efficacy is limited because of low bioavailability due to poor absorption and rapid metabolism. Therefore, it required further improvement strategies. The combination of curcumin and resveratrol has synergistic anticancer activity in colon cancer cells. The combination of Curcumin and resveratrol was evaluated for anticancer activity on Hepal-6HCC cells. Both induced apoptosis either via intrinsic or extrinsic pathway. Curcumin and resveratrol showed synergistic anticancer effect which is associated with reactive oxygen species (ROS) generation, downregulation of X-linked inhibitor of apoptosis protein (XIAP) and surviving (anti-apoptosis gene). Curcumin and resveratrol in combination provided novel anticancer treatment strategy for liver cancer. [5]

7) *Eleutherine palmifolia* and *Macrosolen cochinchinensis* in cervical cancer

Eleutherine palmifolia
(Dayak onion)

Macrosolen cochinchinensis
(Starfruit Mistletoe)

The anticancer activity of combination of Sabrang onion (EP) and Starfruit mistletoe (MC) ethanolic extracts have been reported by the authors. Combined ethanolic extract of both plants induced apoptosis in HeLa cervical cancer cell. The cytotoxic potential of EP and MC combination was determined by MTT assay on HeLa cancer cells. The combination test was carried out with each of 16 concentration series below the concentration of IC50.

Strongest synergistic effect (CI-0.15) showed by combination dose EP 22.62 µg/ml and MC 23.3 µg/ml as compared to other combination doses. Some other combination doses that have the synergistic effect was 23.3 µg/ml MC and 11.31 µg/ml EP; 23.3 µg/ml MC and 16.96 µg/ml EP. Both plant extract inhibited the cell cycle in G0-G1, G2/M and S (synthesis) phase when used in combination.[6]

8) Clove and cinnamon extracts

Syzygium aromaticum
(Clove)

Cinnamomum verum
(Cinnamon)

Clove and cinnamon both are antioxidants and produced anticancer activity when evaluated by MTT assay. Aqueous extract of clove/cinnamon possessesstrong cytotoxic activity on liver cancer cell line Hep G2 against 5-fluorouracil as reference. Cell inhibition was produced after 24 hrs. The cytotoxicity of clove and cinnamon is due to Pinocembrin flavonoid which producesapoptosis cancerous cell and lipid peroxidation.Another flavonoid present in clove and cinnamon is apigenin, which possess antioxidant and anticancer properties. [7]

Synergistic effect of plant extracts when given with anticancer agents

This sections deals with the combinations of plant extracts with drugs already proven therapeutic activity.

1) Berberine and Rapamycin

Berberis arista

Rapamycin is potent antifungal but it was investigated as an immunosuppressant. It shows powerful anti-proliferative effects because it targets (m-TOR) signalling pathway (serine/threonine kinase) which is important for normal and cancer cell growth.

Berberine, an alkaloid extracted from various plants. Berberine used for the treatment of various human cancer cells such as liver, lungs, stomach, colon, skin, oesophagus, brain, bones and breast cancer. Berberine suppress the growth of cancer cell cycle, inhibit synthesis of DNA and proteins and reduces the topoisomerase activity. Berberine alkaloid also reported that it enhances cancer cell apoptosis via apoptotic gene expression regulation and decreasing transmembrane potential of mitochondria.

Anticancer activity of combined berberine and rapamycin was evaluated on hepatocellular carcinoma (HCC). Combination of berberine and rapamycin synergistically suppress the m-TOR signalling pathway and increased the efficacy of chemotherapy for HCC. Cytotoxic effect of rapamycin on HCC was observed to maintain by berberine at a lower concentration. Over expression of CD147 was found in cells co-treated with berberine and rapamycin which significantly inhibit down-regulation of phosphorylated mTOR expression and decrease cell death. [5]

2) Tea Catechins and Doxorubicin

Camellia sinensis (Green tea leaves)

Green tea contains polyphenol Epigallocatechin-3-O-gallate (EGCG), has a variety of physiological and pharmacological effects.

Catechin decrease the level of a membrane transporter i.e. P-glycoprotein, that pumps a wide range of xenobiotics, in DOX-resistant hepatocellular carcinoma cells. Catechin also reported to inhibit the expression of multidrug resistance 1 (MDR1) mRNA. When doxorubicin given in combination with EGCG. P-glycoprotein efflux pump activity inhibited by epicatechin gallate, which result in accumulation of doxorubicin intracellularly. Doxorubicin produced cardiotoxicity by suppressing oxidative stress, inflammation and apoptotic signals as well as by activating pro-survival pathways, which is protected by EGCG which act as cardio-protective against doxorubicin.[5]

3) Grape Seed Extract (GSE) with doxorubicin

Vitis vinifera

Grapes seed extract (GSE) is a dietary supplement made by removing, drying and pulverizing the bitter tasting seeds. GSE is a natural substance available in capsules and tablets (100-500 mg) sold as an over-the-counter product in United State. GSE used to treat heart issues (atherosclerosis). GSE has antioxidant properties because it contains proanthocyanidin. The antioxidant capacity of GSE has been reported to be greater than known antioxidants such as vitamin C and E.

GSE inhibit the growth of cancer cells by inhibiting the aromatase enzyme which is responsible for the conversion of androgen to estrogen in aromatase transfected MCF-7 breast cancer cells. When GSE given in combination with doxorubicin. GSE exerted a synergistic anticancer effect by decreasing aromatase enzyme activity and inhibiting the growth of estrogen-receptor expressing MCF-7 cells. [8]

4) Curcumin and 5-fluorouracil plus cisplatin (FP)

Curcumin

FP is anticancer drug which inhibit enzyme activity, prevent DNA synthesis and promote apoptosis in cancer cells. But anticancer drugs produce resistance and severe side effects.

Curcumin elicits anti-proliferative effect and induced apoptosis in various types of cancer, including lungs, ovarian, oesophageal and liver cancer. Curcumin acted on MDSCs i.e. myeloid-derived suppressor cells, inhibit their activation, promote their differentiation and interfere their interaction with cancer cells and suppress growth of cancer cells. In human gastric cancer cells, curcumin reported to protect against chemoresistance by downregulating nuclear factor κ-light chain enhancer of activated B cells (NF-κB) and subsequent NF-κB mediated Bcl-2 and Bcl extra-large anti-apoptotic genes in the SGC 7901 human gastric cancer cells. Curcumin down regulate the activity of serine/threonine-protein kinase PAK1 and expression of cyclin D1. Therefore, curcumin control proliferation and invasion of gastric cancer cells in human. Curcumin produces synergistic effect when given in combination with doxorubicin in MCF-7 cells via inhibition of NF-κB and epidermal growth factor activity.

When FP given in combination with curcumin and evaluated for cytotoxic effect on gastric cancer MGC-803 cells. FP anticancer activity increased by Curcumin because it decreases cell viability, inhibit colony formation and cell migration. Curcumin induced apoptosis because it activates caspase -3/8, down regulate B-cell lymphoma-2 (Bcl02)and up-regulate Bcl-2-associated X protein Bax. Therefore, curcumin has synergistic anticancer activity when given in combination with FP. [9]

5) Neem (*Azadirachta indica*) and Cisplatin

Azadirachta indica

Neem has various activities like it act as tumor suppressive, anti-proliferative, immuno-modulator and produce apoptosis in cancerous cells. Neem exerts antioxidant properties because it decreases TNF-α, increase IFN-γ and modulate antioxidant enzyme (glutathione S-transferase GST).Neem arrest the cell cycle because of p53-dependent p21 accumulation, down regulation of regulatory proteins of cell cycle i.e. cyclin B, cyclin D1 and proliferating cell nuclear antigen (PCNA). Neem produces apoptosis via both intrinsic and extrinsic pathways. Cisplatin is a chemotherapeutic agent which contains platinum, used to treat number of cancers and solid malignancies. But use of cisplatin is limited because it produces various side effects like nephrotoxicity, ototoxicity (hearing loss), haemolytic anaemia, electrolyte disturbance, nausea and vomiting. Cisplatin when given in combination with ethanolic neem extract for HeLa cells (cervical cancerous cells) and MCF-7 (breast cancer cells)showed enhanced growth inhibitory effect in comparison to individual doses. Cell viability was analysed by treating MCF-7 and HeLa with different sub-lethal doses of cisplatin and ethanolic neem extract for 48 hrs and 24 hrs respectively. Cell viability decreased when cisplatin given with neem extract. Therefore, therapeutic index of cisplatin was potentiated by Neem. [10]

6) *Lycium barbarum* (Goji berry) and Doxorubicin

Lycium barbarum

Water extracts of *L. barbarum* fruits, contains polyphenols and polysaccharides which act as antioxidant.Cytotoxic effect of L. barbarum fruit extract (LBE) and its combination with doxorubicin was evaluated by MTT assay on MCF-7 and MDA-MB-231 breast cancer cells.The combination of LBE and doxorubicin showed synergistic cytotoxic effect on MCF-7 and MDA-MB-231 cancer cells. Cell viability was much lower with the combination treatment than with doxorubicin alone. *Lycium barbarum* fruit (Goji berry) extract is a very good partner in the combination treatment with doxorubicin because it increases the antitumor activity i.e. the therapeutic effectof doxorubicin and it reduces the risk of dose-dependent cardiotoxicity (an adverse effect of doxorubicin in treatment of breast cancer). [11]

Table1: Constituents, part used and activity of different plant extract combinations

Sl.No.	Plant Combination	Families	Part used	Active constituents	Action performed	Reference
1.	*Curcuma Longa* + *Tinospora Cordifolia*	Zingiberaceae Menispermaceae	Rhizome Stem	-Curcumin , demethoxycurcumin -Berberine, tinosporide, tinosporin	Anticancer	1
2.	*Corydalis yanhusuo* + *Curcuma wenyujin*	Papaveraceae Zingiberaceae	Whole plant Rhizome	-Dehydrocorybulbine (DHCB), Tetrahydropalmatine (THP) -Curcuminol , wenyujinoside	Anticancer	2
3.	*Coptidis chinensis* + *Evodia rutaecarpa*	Ranunculaceae Rutaceae	Rhizome Fruits	-Berberine, palmatine, coptisine -Synephrine, evodiamine	Anticancer	3
4.	*Descurainiae sophia* + *Peucedani praeruptorum*	Brassicaceae Umbelliferae	Flixweeds Roots	-Scopoletine, scopoline, xanthtoxol, xanthtoxin -Praerutorin A & B, raeroside, Furanocoumarin glycosides	Anticancer	4
5.	*Zizyphus Jujuba* + *Camellia sinensis*	Rhamnaceae Theaceae	Fruits, seeds Leaves	-B-sitosterol, daucosterol, heptadecanoic acid, tetracosanoic acid, rutin&d- glucose -Caffeine, epicatechin, theophylline, epigallocatechin	Anticancer	5
6.	*Curcuma longa* + *Polygonum cuspdatum* + *Rheum officinale*	Zingiberacea Polygonaceae polygonaceae	Tuberous Rhizome Roots	-Curcumin -Gallic acid, tryptophan catechin, emodin -Anthraquinone, lucogallin, eallic acid, rheinotannic acid, catechin	Anticancer	5
7.	*Eleutherine palmifolia* + *Macrosolen cochinchinensis*	Iridaceae Loranthaceae	Roots Berries, leaves	-Alkaloids, glycosides, steroids , flavonoids and tannin -Gallic acid, orientin, rutin, quercetin, vicenin	Anticancer	6
8.	*Syzygium aromaticum* + *Cinnamomum verum*	Myrtaceae Lauraceae	Flower buds, leaves, stem Bark	-Eugenol, β-caryophyllene, sesquiterpenes, oleanolic acid, crategolic acid -Cinnamaldehyde, eugenol, carotenoids, tannins, mucilage.	Anticancer	7
9.	*Centaurea ainetensis* + *Achillea falcate*	Asteraceae Asteraceae	Ground flower head Flower	-Salograviolide, sesquiterpene lactones, guaianolide -Coumarin, terpenoids, sterol, flavanoids	Anticancer	12
10.	*Salvadora presica* + *Nigella sativa* + *Aloe vera*	Salvadoraceae Ranunculaceae Asphodelaceae	Stem Seeds Leaves	-Salvadourea, vitamin C, saponins, alkaloids, steraric acid, flavonoids, lignans, glycosides. -Thymohydroquinone, dihydrothymoquinone, thujene, β & α-pinene, cymene, carvacrol. -Vitamin A, C & E, saponins, lignin, salicylic acid, sugar, anthraquinone, amino acids.	Anti microbial Anti-proliferative Antioxidant	13
11.	*Terminalia catappa* + *Colocasia esculenta*	Combretaceae Araceae	Leaves Leaves	-Linoleic acid, oleic acid, palmitic acid, stearic acid -Flavanoids, terpenoids, β-sitosterol, steroids	Anti microbial Antioxidant	14
12.	*Acacia nilotica* + *Murraya koenigii* + *Eucalyptus* + *Psidium guajava*	Mimosaceae Rutaceae Myrtaceae Myrtaceae	Leaves Leaves Leaves Leaves	-Methionine, threonine, ethylgallate, catechin, potassium, magnesium, zinc, copper. -Sabinene, β-pinene, limonene, α-humulene, β-caryophyllene, bornyl acetate. -Eucalyptol, p-cymene, α-terpinol, α-pinene. -B-sitosterol, uvaol, aleanolic acid, urosolic acid.	Anti microbial Antiplaque	15
Plant combination with anticancer drugs						
13.	*Berberis arista* + Rapamycin	Berberidaceae	Root, stem, leaves, fruits	-Berberine, berbamine, taxilamine, jatrorrhizine	Anticancer	5
14.	*Camellia sinensis* + Doxorubicin	Theaceae	Leaves	-Caffeine, epicatechin, theophylline, epigallocatechin	Anticancer	5

Sl.No.	Plant Combination	Families	Part used	Active constituents	Action performed	Reference
15.	*Vitis vinifera* + Doxorubicin	Vitaceae	Seeds	-Catechin, Epicatechin, procyanidin, proanthocyanidine,	Anticancer	8
16.	*Curcuma longa* + 5-fluorouracil + Cisplatin	Zingiberacea	Tuberous	-Curcumin	Anticancer	9
17.	*Azadirachta indica* + Cisplatin	Meliaceae	Leaves, fruits, seeds	-Nimbin, nimbinene, nimocinol, β -sitosterol, 6-desacetyllnimbene, nimbandiol	Anticancer	10
18.	*Lycium barbarum* + Doxorubicin	Solanaceae	Berry	-Betaine, beta-carotene, zeaxanthin, riboflavin, thiamine, ascorbic acid,	Anticancer	11
19.	*Rauwolfia vomitoria* + Carbaplatin	Apocynaceae	Roots	-Yohimbine, reserpine, rauvoxine, rescinnamine, deserpidine.	Anticancer	16
20.	*Clinacanthus nutas* + Gemcitabine	Acanthaceae	Leaves, stems	-Triterpenoids, 7 C-glycosyl flavones, phenolic acid, phaeophorbide and chlorophyll derivstives	Anticancer	17
21.	*Eucalyptus camaldulensis* + Gentamycin / Ceftriaxone	Myrtaceae	Leaves	-Eucalyptol, p-cymene, α-terpinol, α-pinene.	Antibacterial	18
22.	*Calendula officinalis* + Cefotaxime	Asteraceae	Flower	-Triterpenoids, flavonoids, coumarin, quinines, carotenoids.	Antibacterial/ Antimicrobial	19
23.	*Thymbra spicata* + Ampicillin, cefotaxime, amikacin, ciprofloxacin	Lamiaceae	Leaves	-β- myrcene, p-cymene, terpinene, trans-caryophyllene, carvacrol.	Antibacterial	20
24.	*Canarium odontophyllum* + Oxacillin / linzolid	Burseraceae	Leaves	-Ellagic acid, vanillic acid, catechin, epicatechin gallate, anthocyanides	Antibacterial	21
25.	*Inula viscosa* + *Anacyclus valentinus* + Getamycin, oxacillin	Asteraceae Asteraceae	Leaves, flowers Leaves, flowers	-Fokienol, nerolidol, globulol, valerianol, caryophyllene oxide -Carene, spathulenol, decanoic acid, cardinene, anethole, aromadendrene	Antibacterial	22
26.	*Alternanthera pungens* + Ampicillin / Streptomycin	Amaranthaceae	whole plant	-Lupeol acetate, α-amyrin acetate, quercetin, β-sitosterol, α-spina sterol, stigma sterol.	Antibacterial	23
27.	*Citrullus colocynthis* + Ampicillin / Streptomycin	Cucurbitaceae	Fruit, leaves	-Cucurbitacins, saponarin, anthranol, cardiac glycosides, tannins, flavanoids.	Antibacterial	23
28.	*Leucas aspera* + Ampicillin/ Streptomycin	Labiatae	Flower, root	-Triterpenoids, oleanolic acid, ursolic acid, b-sitosterol, nicotine, sterols, glucoside, diterpenes.	Antibacterial	23
29.	*Gomphrena celosioides* + Ampicillin/ Streptomycin	Amaranthaceae	Whole plant	-Aurantiamides & its acetate, alkaloids, tannins, flavanoids.	Antibacterial	23
30.	*Helianthus annus* + Ampicillin/ Streptomycin	Asteraceae	Leaves	-Carbohydrates, flavanoids, saponins, tannins, alkaloids, phytosterol, triterpenoids, fixed oil.	Antibacterial	23
31.	*Ipomoea pestigirdis* + Ampicillin/ Streptomycin	Convolvulaceae	Leaves	-Ergoline alkaloids, indolizidine, nortropane alkaloids, flavanoids, glycolipids, lignin, triterpenes.	Antibacterial	23
32.	*Digera muricata* + Ampicillin/ Streptomycin	Amaranthaceae	Leaves	-Flavonoids, alkaloids, terpenoids, saponins, coumarins, tannins, anthraquinone, cardiac glycosides.	Antibacterial	23
33.	*Solanum quitoenes* + Ampicillin/ Streptomycin	Solanaceae	Fruits	-Carotenoids, chlorogenic acid, flavanol glycosides, ascorbic acid, methyl butanoate.	Antibacterial	23

CONCLUSION

The chemical extracts derived from plants have been used to treat human diseases as they offer many advantages in the following manners: 1) The treatment is inexpensive, non-toxic, eco-friendly and a green strategy; 2) the plant extract provide holistic treatment to carcinogenesis; 3) the synergistic effect of different plant extract combinations provides boosted action at the same dose; 4) the patient compatibility is more with herbal treatment as compared to drugs. With large diversity of plants available for exploration, it is evident that these herbal extracts, with a potential to treat cancer, can transform the cancer therapy. Therefore, combining the herbal and modern medicine is a promising approach in order to bring revolution in the treatment of cancer.

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