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Herbal Technology: An Emerging Approach for Treatment of Colon Cancer

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KEYWORDS

Abstract: Conventionally used drug for a treatment of life-threatening disease like cancer gives lighter therapeutic response along with high rate of adverse effects on normal cells, leading to insufficient activity over the tumor cells. These side effects of drug agents over normal cell causes restriction to increase the dose for proper targeting over the tumor cells. The less quantity drug for tumor cell develops resistance over it which causes lacking of response for prevention and treatment of cancer. So herbal agent could be better beneficial for targeting on tumor cell with lighter side effect. The various herbal agents will be discussed as per review that can be beneficial for treatment of colon cancer. A Comprehensive review.

Objective: To describe various safer herbal drugs and herbal technology with reduced adverse effects which can be implemented for treatment of cancer.

Method: Data for review were collected from, PubMed, Science Direct, Medline using the following key-words: 'cancer', 'introduction', 'drug resistance', 'challenges in treatment of cancer', 'overview of colon cancer', 'novel herbal drugs of treatment of cancer', and 'recent advances in herbal technology for colon cancer'.

1. Introduction –

Cancer, a secondary leading cause of death in the world, is a progressive disease which can be diagnosed as uncontrolled cell growth and cell division. The cases of cancer over the worldwide is also increasing in an elevation manner. Cancer, a life threatening disease that is affecting the human health and normal life processes[1]. If we discuss about the previous scenario of this particular disease in India, In the year 2018, reported cases in India were 1.15 million new cases with 784,821 deaths (Cancer statistics Available from URL: http://cancerindia.org.in/cancer-statistics/ (Last Accessed on 07 October, 2020)). Since the last few years , the treatment of cancer works effectively with various technologies like surgery, chemotherapy, and radiotherapy. The use of these treatment strategies can be implemented individually or in combination for effective impact on tumor cell[2].

Generally tumors with initital growth or benign tumors are treated with surgery as well as radiation therapy but distributed tumors or malignant type of cancer like colon cancer , liver cancer, prostate, breast cancer requires chemotherapy for its treatment[3]. Chemotherapeutic agents implemented for prevention and treatment of cancer works by inhibiting the growth of cell, restriction of cell division, and selective attack on mitotic spindle, which physiologically functions as replication and division of cell[4]. Due to heavier toxic and side effect of chemotherapeutic agent, limited dose is applicable to the patient, which is less sufficient for the treatment of tumor. This causes insufficient treatment and escalation

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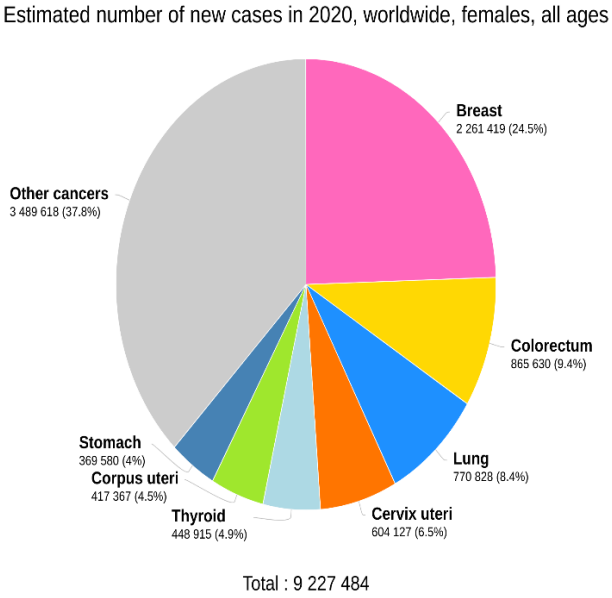
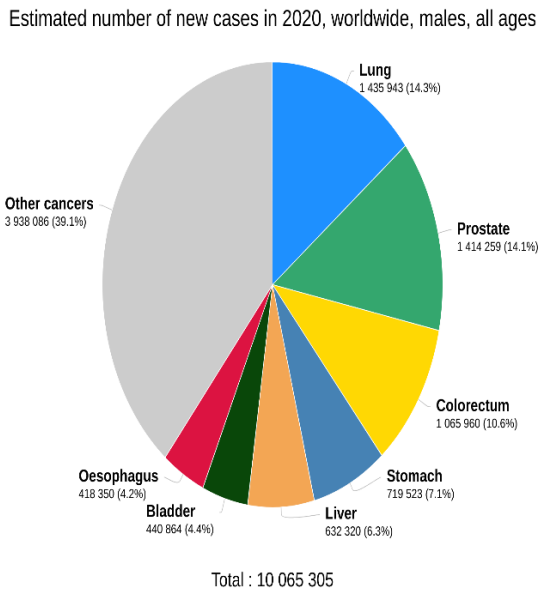
of dose is restricted due to its side effects to the normal cell and limited dose of drug is delivered[5].

Colorectal cancer (CRC), the third most frequent cancer type and leads to the highest number of cancer-related deaths. The recent development in gene sequencing and molecular biology techniques has discovered the several mechanisms identified for drug resistance. The development of these resistance led to approaches towards novel drugs to reduce the Multi Drug Resistance(MDR) [6]. In recent times, natural compound which are obtained from alkaloids glycoside, etc are effectively being used as potential herbal medicine for the treatment of cancer which also reduces drug resistance. As wide varieties of anticancer drugs are obtained from natural products. So herbal medicines is playing an important role in the cancer therapies with reduced multidrug resistance[7].





2. CHALLENGES IN THE TREATMENT OF CANCER

Over-the-year the treatment of cancer is found to be a major challenge. Previous assumptions for treatment of cancer was based over the fact that all somatic cells have own potential for malignant development[8]. Another major reason for failure in the treatment of the answer is that the basic normal cell in its whole life is in the process of development with self-regulation and differentiation, which is somehow similar to the developing cancer cell process so chemotherapeutic agent harmful xenobiotics may also provide harmful effect to the basic normal cell with reduced failure action over the cancer cell[9]. Beside of these and another major factor in treatment of cancer is lack of specificity towards the proliferating cancer cells that's why it affects proliferating cancerous cell as well as normal cell which cause inhibition in the growth of that normal cell which may develop serious adverse effect and sometimes lead to death of an individual[10][11]. Another major issue with chemotherapeutic drugs is that it has low / limited bioavailability of drugs as many of the drugs used in treatment of cancer has low bioavailability[12]. The tumor progression course occurs in a branch manager rather than in a linear manner and the development of cell occurs inside the cell as well as in the form of clones, this makes its identification and treatment difficult[13][14].

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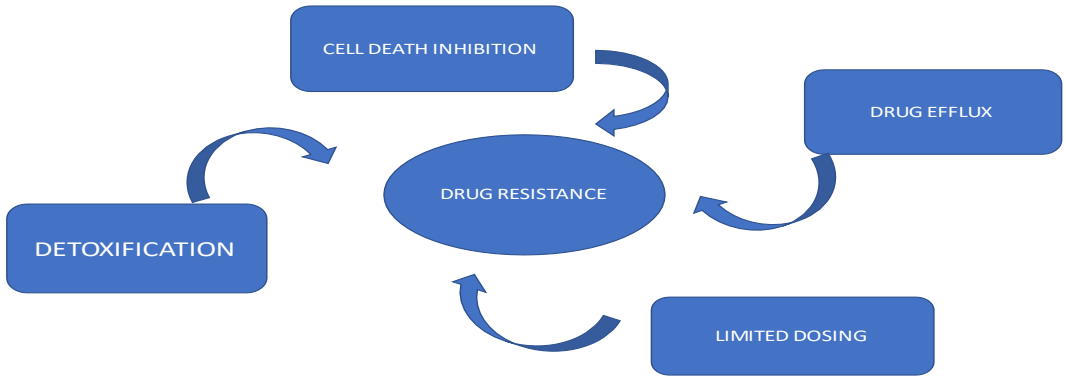

Fig 2. Describing various mechanism of drug resistance

3. Natural Bioactive for The Management of Colon Cancer

The various GI disease like Ulcerative Colitis (UC), Inflammatory Bowel Disease (IBD) is a destructive lifelong chronic disease[15]. The mucosal immune system functions as the centre effector for the injury and GI inflammation. Whereas Cytokinin's and Interleukins modulates inflammation in the lower alimentary canal[16][17].

Organisms in the ecosystem producing secondary metabolites with targetive purpose to gain innovative advantages. To enhance the possibility to discover lead compound for newer drug development, the potential pharmacological tool is bio active natural product for synthesis of newer drug entity[18]. The various natural vectors for the management of colon cancer can be explained in the below examples;

a. The Oxaliplatin and Digitoxin combination exhibit synergism otherwise highly drug resistant to HT29 cell line[19].

b. A plant flavonoid i.e. fisetin induces apoptosis in colon cancer cells by inhibition of Cox-2 and anti Kappa-B signaling pathway. This shows evidence that fisetin flavonoid induces apoptosis as well as suppresses the growth of colon cancer cell[20].

c. The contribution of Plukenetione-A to the antitumoral activity of the Cuban Propolis was found as targeting Topo-isomerase 1 and DNA polymerase[21].

d. Curcumin(di-fenuloylmethane), a natural plant product, functions in the prevention by targeting multiple signaling pathway[22].

e. Colon targeting of rhubarb extract prevents free anthraquinone absorption in the upper GI tract[23][24].

4. HERBAL TECHNOLOGY IN TREATMENT OF COLON CANCER

In recent times, the treatment of cancer from natural products are widely targeted[25]. The main source for the occurrence of these natural products are plants which are majorly preferred for medicine. If the compound contains more number of active compound that it will produce drug interaction, with adverse effects and reduced activities. Hence, various types of targeting carriers can be used for encapsulation and delivery of drug[26], in which the anti-cancer bioactive compound or chemotherapeutic drug in combination with herbal compound encapsulated to develop in a type of formulation[27]. The larger surface area v/s volume ratio permits alteration in nanoparticles for its targeting functionalization moieties[28]. The limitations of herbal therapy it could notice therapeutic concentration range but therapeutic effect cannot[29].

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Type of nanomedicines	Targeting System	Herbal-Drug Composition	Major Outcomes	Ref
Herbal & chemotherapy	HA-PLGA NPs	Curcumin/ Camptothecin	Synergistic effect of this combination over Colon-26 cells has great impact on tumor cell targeting.	[30], [31]
Herbal & genes therapy	PLGA NPs-embedded hydroge	Camptothecin/ CD98 siRNA	Tumor growth suppression due to synergistic effect of therapy over Colon-26 cells.	[32], [33]

5. RECENT DEVELOPMENT IN COMBINED HERBAL NANOMEDICINE FOR COLORECTAL CANCER

In cancer treatment, Camptothecin, a chemotherapeutic drug that had shown a better anti-cancer activity together during pre-clinical trial studies, but due to resistance in escalation of dose, it gives lesser efficacy with side effects over normal cells. So, combinations of Camptothecin and Curcumin in HA functionalised PLGA [poly D,L-lactic-co-glycolic acid] NPs[Nanoparticles] observes a effective targeting response over colon cancer cells, and this synergistic effects over colon-26 cells were clearly observed[30], [31].

Drug delivery of a particle or pharmaceutical compound on reference to nanomedicine is consider as nanometre technology of complex system , which contains two or more than two components enclosed, one which is active pharmaceutical ingredients[34], whereas formulation of nanoparticles of itself drug are also possible[35][36][37]. The development of this new system helps in smart targeting, diagnosis, prevention, and treatment of disease[38]. The major function of nanoparticle is as carrier transporter for a drug moiety[39].

Camptothecin and Curcumin can also be formulated with chitosan polymer to produce Nanoparticles. The observation confirms the simultaneously and controlled release of Camptothecin and Curcumin[40] by polymeric matrix which can be further taken up by the cancer cells[30].

Curcumin (Curcuma Longa Linn) herbal medicinal agent which contains its main as 77% beside of which it also contains demethoxycurcumin as well as bis-demethoxycurcumin. Both compounds belongs to category of diarylheptanoids[40]. The above three compounds are referred to as curcuminoids. Curcumin has crystallised behaviour with bright yellow-orange colour. It is mainly used as colouring, flavouring agent and food additives. It has great potential activity in anti-cancer herbal technology[41][42], [43].

According to camptothecin action mechanism, camptothecin act by binding at the DNA Complex of topoisomerase 1, which causes collection of DNA strands which breaks upon replication causing death of cell at S phase of the cycle. Without camptothecin, the complex passes through the various critical conditions like replication of DNA, transcription, recombination, chromatin fibres assembly followed by chromatin segregation[44], [45].

Topoisomerase I (Top1) is a class IB topoisomerase that binds to replicate the structure of DNA and separate single stand initially to form separated DNA strand with the help of phosphor-tyrosyl bond at the 3’ end. The self-evacuated ligation (5’ hydroxyl) restores the double stranded DNA[46]–[48]. Topoisomerase I mediated separation at single stranded ribonucleotides entangled in DNA strand may take to mutation as well as instability of genome[49], [50].

Chemical structure of Camptothecin Camptotheca Acuminata (Camptothecin)

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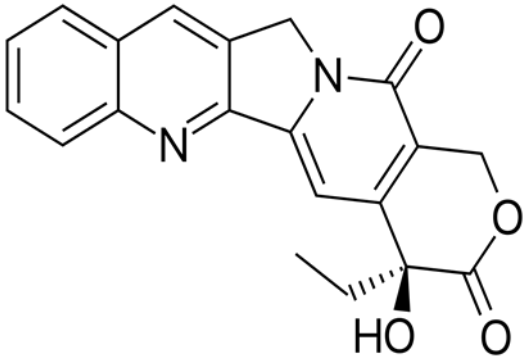
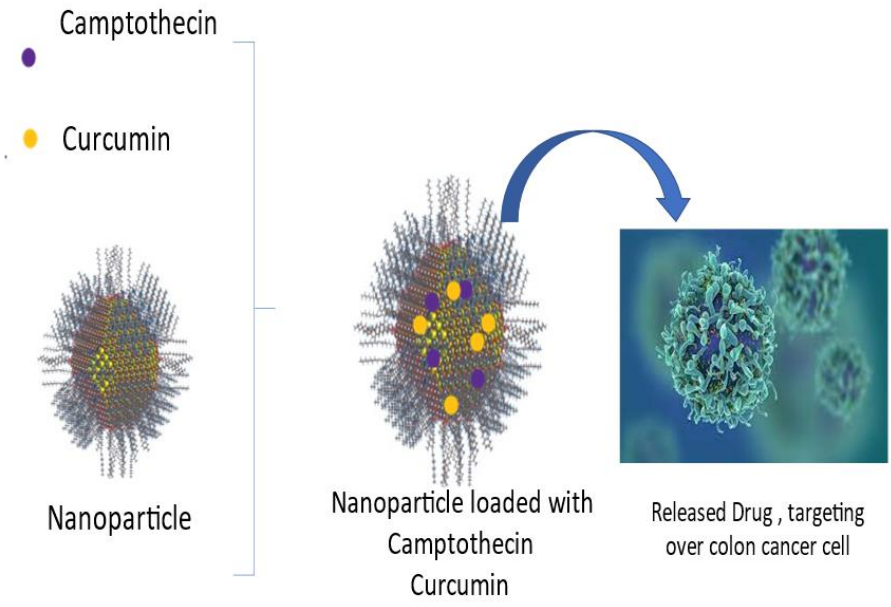


Recently, combination of Camptothecin (a natural topoisomerase inhibitor[51]) and a gene (siCD98RNA) has observed as a better targeted drug delivery system effective against colon cancer treatment. The above formulation was loaded inside CD98 Fab' functionalised PLGA Nanoparticles[33].



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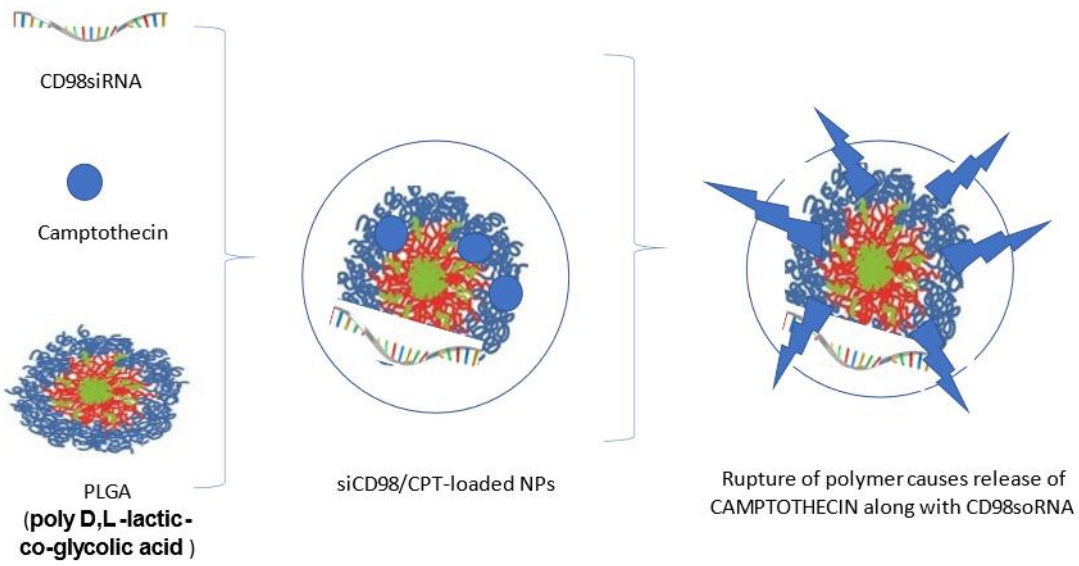

Fig 4. Showing release of Camptothecin and gene Nanoparticle (siCD98/CPT).

Efficacy of herbal medicines for colorectal cancer (in-vivo models)		
Effect On Cell	Mechanisms	References
Increased depth in crypt and growth-inhibitory effects.	Myeloperoxidase activity is inhibited.	[52]
Cell viability Inhibited.	Decreased VEGF, MMP-3, MMP7, MMP-8, MMP-9, TNF, MMP-1, and MMP-13 protein expression	[53]
Significantly reduced histological damages.	Not mentioned	[54]
Not mentioned	Suppression of proliferation, formation of pheres, which causes nuclear translocation of βeta-catenin βeta-catenin signaling Mitochondrial mediated apoptosis due to elevation in p53.	[55]
Approximately 2 times increase apoptosis of tumor cell	Extra cellular signal regulated kinase (ERK-2) inactivated and ERK-1 inhibited as well as expression of Vascular Endothelial Growth Factor (VEGF)	[56]
Reduction of the basement membrane	Release of Matrix Metallopeptidase -9 as well sa VEGF is blocked	[57]
Apoptosis of human colon cancer cells induces	Reduction in formation of edema linked to devitalzation of Cyclooxygenase-2 which causes expose of promotor analysis	[58]
Not mentioned	NFκB, AP-1, NF- Il-6 modulated	[59]

Scientific name	Model	Parts used	Active moeity
Vitis vinifera	In vivo (murine) Caco-2	Seed	Procyanidins
	In vivo Human Colorectal adenocarcinoma Cell line SW480	Seed	
	In vivo	Skin	4′-Geranyloxyferulic acid
	In vivo (murine)	Seed	Catechin, epicatechin
Camellia sinensis	In vivo (murine)	Leaf	Catechin, epigallocatechin gallate
	In vivo (murine)	Leaf	Not mentioned
	In vivo (murine)	Leaf	Theaflavins
	In vivo (murine)	Leaf	Phenolic compounds (pinoresinol & dihydroxyphenyl Ethanol, p-hydroxyphenyl ethanol)

Efficacy of herbal medicines for colorectal cancer (in-vivo models)

Mechanisms	References
Suppression of sphere formation. Prominin-1 and CD44+ stem cell markers expression over cancer cell.	[60]
Peritoneal macrophages phagocytosis is activation	[61]
Cytochrome c levels also increased by PA treatment independent from p53 status indicating that the induction of apoptosis might be via mitochondria- mediated apoptotic pathway. Nuclear β-catenin and cytoplasmic levels are suppressed	[62]
Retino-blastoma phosphor-protein are deactivated causing induced G1 arrest and expression of Early Growth Response-1	[63]
Oxygen and nutrient transportation is restricted causing decrease in size and growth of tumor cell which leads to tumor necrosis.	[64]

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Efficacy of herbal medici	Scientific name	Model	Parts used	Active moeity	Effect On Cell
References					
[65]	Sasa quelpaertensis	In vivo	Leaf	p-Coumaric acid, tricin	Colony development is restricted.
	Anoectochilus	In vivo	Not mentioned	Kinsenoside	Lymphoid tissues proliferation is stimulated.
[66]	Purple-fleshed potatoes	In vivo Colon cancer stem cells	Fruit	Anthocyanin, β-catenin, cytochrome c	Reproving CSC proliferation of its downstream proteins (c-Myc and cyclin D1), elevated Bax and cytochrome c, mitochondria-mediated apoptotic proteins.
[67]	Phaseolus vulgaris	In vivo	Leaf	Polysaccharides, oligosaccharides	Variation in associated genes causes restriction in cell proliferation due to FE-hgh-CL40 and apoptosis induces.
[68]	Myrtaceae	In vivo (murine)	Leaf	Phenolics, flavonoids, betulinic acid	Tumor angiogenesis is inhibiteds.
[69]					

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Scientific name	Model	Parts used	Active moeity	Effect On Cell	Mechanisms
Wasabia japonica	In vivo	Rhizomes	6-(Methylsulfinyl)hexyl isothiocyanate	Anti-colon cancer properties identified by the induction of autophagy and apoptosis.	Tumor Necrosis factor-, cytochrome-C is activated. Reduced Akt phosphorylation which promotes micro tubules expression.
Spica prunellae	In vivo	Leaf	Rosmarinic acid	Induction of apoptosis and inhibition of cell proliferation and tumor angiogenesis	Inhibition of proliferated cancer cell and blocked phosphorylation of angiogenesis STAT3. This regulates B-cell lymphoma, Cyclin D-1, cyclin dependent kinase 4, VEGFR-2 and VEGF-A expression.
Gymnaster koraiensis	In vivo (murine)	Aerial part	Gymnasterkoreaynes B, C, E, 2,9,16-heptadecatrien-4,6- dyne-8-ol	Reduces inflammation and prevention to cancer	Reduces effect of COX-2 and increases serum IL-6 level.
Allium fistulosum	In vivo (murine)	Edible portions	p-Coumaric acid, ferulic acid, sinapic acid, quercitrin, isoquercitrin, quercetol, kaempferol	Tumor growth which suppressed increased causes survival chances of mice	Expression of molecular inflammatory markers decreases, repression of Matrix Metallopeptidase-9 and Inter-Cellular adhesion molecule.
Annona squamosa Linn	In vivo (murine)	Leaf	Acetogenins (annoreticuin & isoannoreticuin) and alkaloids dopamine, salsolinol, and coclaurine	Tumor cell proliferation and growth is restricted through ROS (Reactive Oxygen Species) formation. This causes release of lactate dehydrogenase.	

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Efficacy of herbal medicines for colorectal cancer (in-vivo models)

Model	Parts used	Active moeity	Effect On Cell	Mechanisms	References
In vivo	Stalk layer	Apigeninidin & luteolinidin	Reduces Proliferation	Act by targeting on p53 independent and p53 dependent pathways.	[70]
In vivo	Leaf and twigs	Sesquiterpene lactone	Carcinogenic cells proliferation restricted.	The NFkB pathway is restricted and inhibits isthe p65(RelA) subunit and the upstream mediators IKKβ and oncogenic K-ras.	[71]
In vivo (murine)	Aerial parts	4′ flacourticin, benzoylpoliothrysoside	Reduces proliferation of cell and pro-apoptotic effect on HCT116 cell.	Generation of ROS causes apoptosis of cell.	[72]
In vivo (murine)	Leaf & fruit	5-O- caffeoylquinic acid Heterosides, , flavonol and flavone.	Restricts proliferation of cancer cell on colon and kidney.	Inhibition of activation of NFκB, activator (AP-1), mitogen-activated protein kinase, PKC (GFR)-mediated pathway. This causes angiogenesis of cell as well as apoptosis and anti- inflammatory effects.	[73]
In vivo (murine)	Aerial parts	Buddlejasaponin IV	Induces apoptosis in colon cancer cells (HT29).	Apoptosis is induces by mitochondria dependent pathway activated by repression of Bcl-2 level of proteinwhich causes activation of caspae .	[74]

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	Scientific name	Sorghum bicolor	Rolandra fruticosa	Flacourtia indica	Cydonia oblonga Miller	Sedum kamtschaticum

Conclusion - To reach the desired action over the cancer cell with lighter degree of side effect as well as adverse effect, the herbal technology is more compatible than traditionally used allopathic anticancer agents. Because due to lesser degree of side effects we can escalate the dose of herbal drugs for proper reach to the cancer cell. But in case of traditionally used allopathic anticancer agents, it produces less therapeutic effect followed by higher side effects. On the other hand, improvisation of herbal technology, which involves the use of various polymers in the formulation and encapsulation of herbal drug that can be implemented for targeting over the cancer cell. These are also beneficial for sustained and controlled release to a specific organ of the body.

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