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METABOLOMICS PERSPECTIVE OF MEDICINAL PLANTS IN TREATMENT OF COLORECTAL CANCER (CRC): A REVIEW

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ABSTRACT

Colorectal cancer (CRC) is the third most serious cancer in man other than prostate and lung cancer, and second most common type of cancer in women right behind breast cancer. It is caused by hereditary, natural and nutritional factors. Many treatments of colorectal cancer are available such as surgery, radiation therapy, chemotherapy, targeted therapy and immunotherapy with many hazardous side effects. Plant derived compounds has the ability to suppress colorectal cancer in different ways such as delaying cancer development, decreasing reliability on radiation therapy and chemotherapy. Secondary metabolites such as terpenoids, alkaloids, flavonoids, phenolics, diosgenin, rosmarinic acid, carnosic acid, luteolin, anthiricin and kaempferol have cytotoxic ability against colorectal cancer. These bioactive compounds can affect the regulation of cell cycle, initiate apoptosis by activating caspase and affect cell signaling pathways. Conventional drugs have been utilized to treat cancer due to their antioxidant nature, anti-invasive properties and anti-angiogenic properties. This review highlights the secondary metabolites of medicinal plants that are used for treating colorectal cancer and their mechanism of action through metabolomics perspective.
Keywords: Colorectal cancer, metabolite, carcinogenesis, medicinal plants, apoptosis.

Introduction

Colorectal cancer is the third most commonly occurring cancer in the world which occurs at the lower part of digestive tract i.e., colon and rectum (Fig. 1). It is the disorder which can be inherited or acquired. Instability of chromosome and microsatellite, CpG island (regions having high concentration of phosphate linked cytosine-guanine pairs) methylator are the three significant mechanisms which occurs in tumorigenesis of colorectal cancer. Inactivation of Adenomatous polyposis coli (APC) gene, mutation of Kirsten rat sarcoma viral (K-ras) oncogene, inactivation of Deleted Colorectal Cancer (DCC) gene and mutation of p53 gene are the multiple hallmarks of colorectal cancer. Certain medical treatments are available for colorectal cancer, mainly chemotherapeutic medications. But these treatments have many side effects such as gastrointestinal problems, sexual infertility, loss of bladder control and sensory neuropathy (Raju *et al.*, 2022) Thus, there is a urgent need to plan and create a new class of compounds with less side effects and having high efficiency to compensate the issues related to surgery, chemotherapy, radiation therapy, targeted therapy and immunotherapy. Plants contain certain bioactive compounds which has a role in inhibition of carcinogenesis of colorectal cancer. Mainly involved phytochemicals are alkaloids, phenolics, terpenoids, flavonoids and glycosides. Secondary metabolites can suppress colorectal cancer growth in different ways such as by apoptosis of cancerous cell, cell cycle arrest, autophagy, inhibiting cellular proliferation, inactivation of Cyclic adenosine 3',5'- monophosphate/ Protein kinase/ cAMP-Responsive Element Binding Protein (cAMP/PKA/CREB) signaling pathway, Extracellular signal-Regulated Kinase (ERK) pathway, Wingless- integrated (Wnt/β-Catenin) signal pathway, induce mitochondrial dependent apoptosis through Bcl-2 associated X protein (BAX) activation, increase reactive oxygen species (ROS) level, suppress Cyclooxygenase-2 (COX-2) and CREB 1 expression, decrease level of Ku 70-protein (Macharia *et al.,* 2022).

Colorectal cancer and Risk factors

Colorectal cancer is the cancer of rectum and colon, which is the fourth most prevalent kind of cancer on the globe with 1.3 million newly diagnosed cases per year. It typically begins as a small clump of cells in the inner surface of the intestinal tract and develops into a non-malignant lesion called an adenoma that can turn malignant relying upon its size and analysis of tissue. Out of the total cases, simple adenoma is 60% and multiple adenomas is 40%. Cancer will develop in about 24% of persons with untreated polyps. The clinical manifestations of CRC are the location, size and existence or lack of metastasis. Abdominal pain, alterations to regular bowel movements, involuntary weight reduction, vomiting, restlessness, malnutrition and swelling in abdominal region are among the sign and symptoms of colorectal cancer, Distal tumors tend to be occulted and result in anaemia because they produce obvious rectal bleeding as opposed to proximal tumors, which can produce mixed blood and stool (Basini *et al.,* 2019).

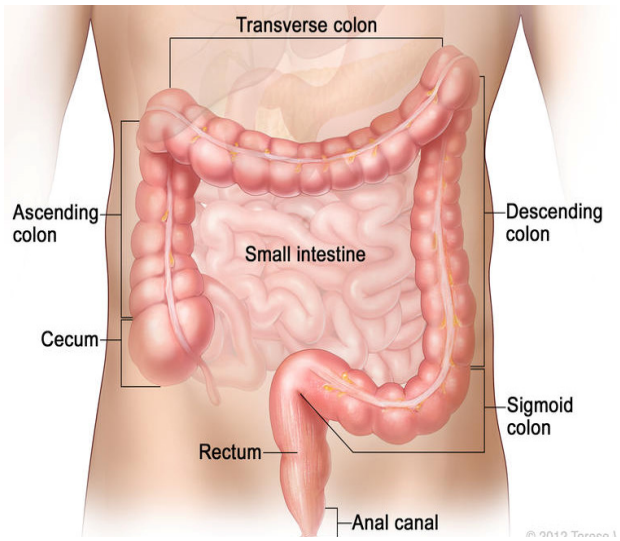


Fig. 1: Sections of the colon (part of digestive tract): Ascending colon; Decending colon; Transverse colon; and Sigmoid colon

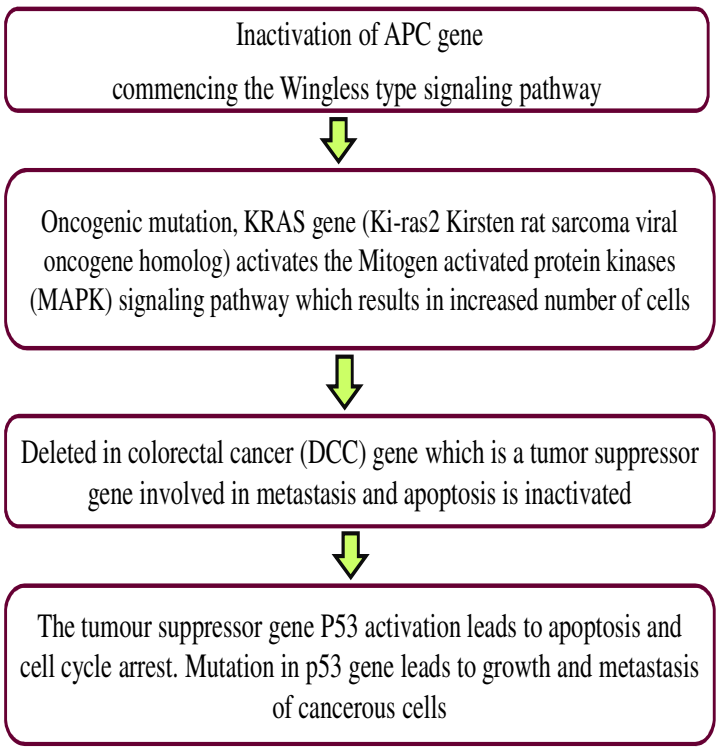
Development of colorectal cancer can be either inherited or acquired. A positive family background appears to play a role in around 10–20% of all colorectal cancer patients, with differed risk based upon the number and seriousness of impacted family members as well as their age at the time of cancer detection. The different ecologically acquired factors which increase colorectal cancer risk are smoking, heavy alcohol consumption, overweight, lack of physical exercise, red and processed meat intake (Dekker *et al.,* 2019). It has been reported that there are certain factors like: random mutation (causes chromosomal rearrangement, DNA error, failure of gene-regulation, control cell cycle etc), apoptosis or mutation in tumor suppression gene/tumor kinases/ tumor proteins or inflammatory state of malignant and pre-malignant lesions causes failure of immune system of body and responsible for hallmark of CRC. Inactivation of APC gene, mutation of K-ras oncogene, inactivation of DCC gene and mutation of p53 gene are the multiple hallmarks of colorectal cancer (Fig. 2 a-c).

Methods of diagnosis and treatment of colorectal cancer in medical science

In both men and women, Colorectal cancer is the most common type of non-skin cancer after prostate, lung and breast cancer) and considered as second leading cause of cancer death in the world. It is an estimated that colorectal cancer have been detected in around 1,49,500 people and approximately 53,000 people were die due to this cancer in 2021 in US in 2021. Many screening tests have been developed to detect the CRC, which may consider as prevention form of cancer along with the detection of colorectal-cancer in early phase. These methods have their own advantages and drawbacks. No specific method or detection technique exists right now in advance science, which gives accurate and acceptable results. Current screening methods are used for the diagnosis of colorectal cancer are mentioned below (Table: 1).

Table 1: Screening methods for the diagnosis of colorectal cancer

Clinical symptoms	Blood in stool, bowel movement change, anaemia, stomachache
Endoscopy	Colonoscopy, Capsule endoscopy
Imaging	Computerized tomography (CT) colonography, Magnetic resonance image (MRI), Locoregional staging, Positron emission tomography (PET) - CT imaging
Blood test	Complete blood count, chemistry profile
Needle biopsy	RAS mutation test, mismatch repair protein (MMR) test



Treatment for Colorectal cancer in medical science uses multidisciplinary approach, which generally includes surgery, radiation therapy, gastroenterological treatments (covers gastro-intestinal tract disorder). Further treatment recommendations also depand on many factors like: type and the stage of cancer, age of the patients, side effects of treatment plan/ medications, nutritional status of patients etc. The common types of treatment methods used to treat colorectal cancer are depicted below in Table 2.

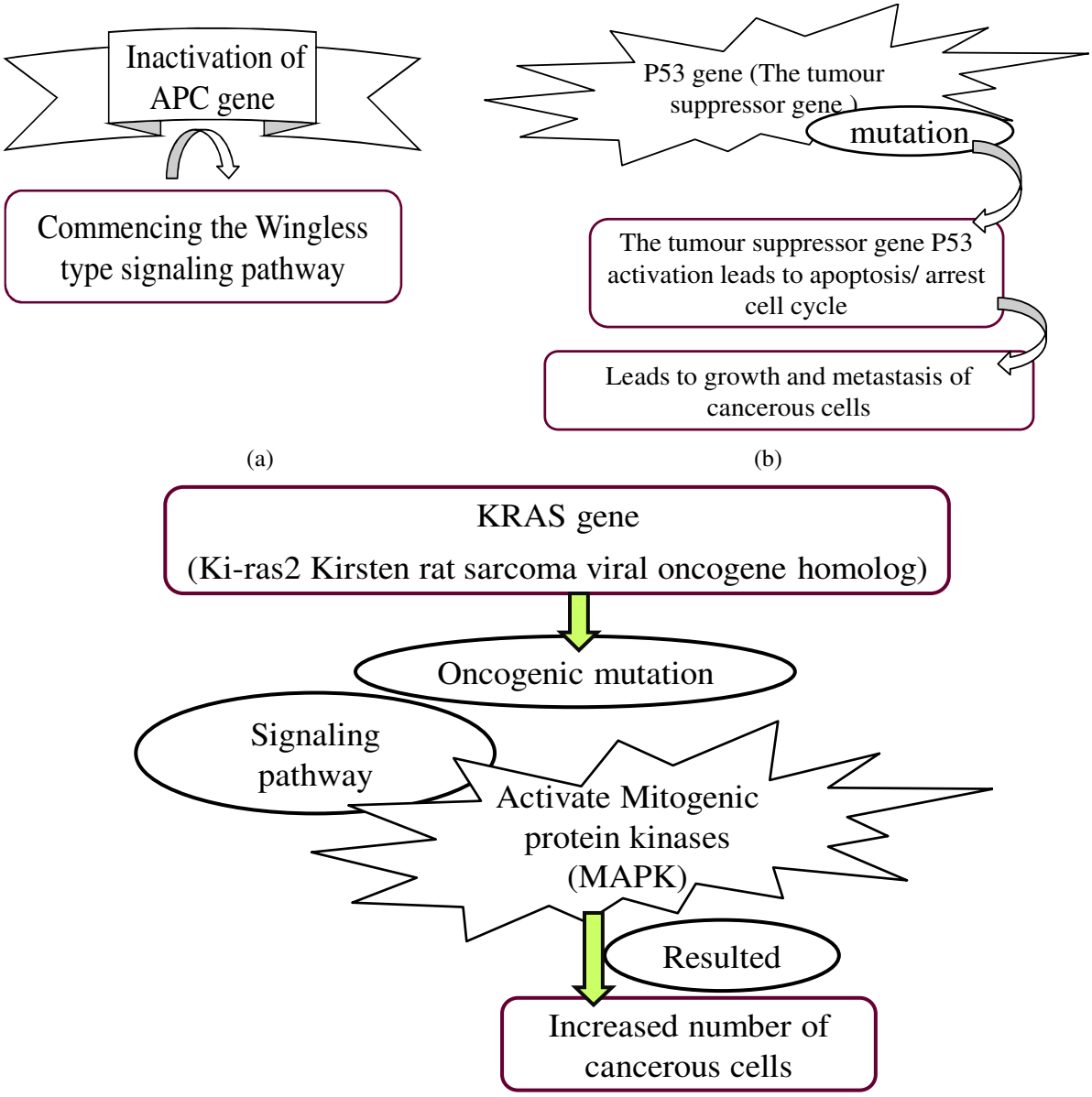


Fig. 2(a-c): Genome instability and inflammation: responsible factors of pathogenesis of Colorectal cancer (CRC)

Table 2: Methods of Colorectal cancer treatment in medical science

S. No.	Treatments			Side effects of treatment
1.	**Surgery or Surgical resection**	Abscission of the tumor along with some nearby normal tissues	Surgical options : Laparoscopic surgery, colostomy, Radiofrequency Ablation (RFA)	Pain and discomfort in the surgical area, diarrhea or constipation
2.	**Radiation therapy**	Radiation oncologists uses high energy radiations to kill cancerous cells	Radiation therapy options: external beam radiation therapy (EBRT), stereotactic radio-surgery (SRS), intra-operative radiation therapy (IORT), Internal radiation therapy(branchy-therapy).	Fatigue, mild skin reaction, stomach distress, rectum hemorrhage or infertility
3.	**Chemotherapy**	Uses medicines to kill cancerous cells, prevents the growth, division and production of new cancer cells	Medications options: fluorouracil (5-fu), qxaliplatin (eloxatin), trifluridine/tipiracil (lonsurf), capecitabine (xeloda), irinotecan (campotosar).	Mouth sore, diarrhea, nausea, vomiting and loss of hair

4.	**Targeted therapy**	Treatment which specifically targets proteins and genes which help cancers cells for their growth and division Prevents spread and development of cancer cells and also minimize harm to normal cells	Targeted therapy options: Ziv-aflibercept and ramucirumab (braf) gene inhibitor (eg. Encorefenib); vascular endothelial growth factor (vegf) inhibitors (eg. Bevacizumab); and epidermal growth factor receptor (egfr) inhibitors (eg. Panitumumab and cetuximab)	Rashes on face and upper body
5.	**Immunotherapy**	Strengthens the ability of immune system to fight against cancerous cells	Possible checkpoint inhibitors used in immunotherapy: pembrolizumab, nivolumab, dostarlimab, ipilimumab	Diarrhea, stomach ache, itchiness and disturbed appetite, breath shortness

Plant- derived metabolites in colorectal cancer treatment

The biggest challenge in cancer treatment today is eliminating tumour cells without causing any harm to healthy cells. Testing chemotherapeutic substances and screening crude plant extracts are required in order to create anticancer medications from natural resources such as plants. Therefore, it is desirable to have access to natural products with more efficacy and fewer adverse effects. Medicinal herbs are essential for the treatment of cancer because they contain a variety of chemical constituents that can be used to identify new cancer-fighting chemicals. Secondary metabolites have biological impacts on hematopoietic cells, lipids, and circulatory systems, as well as anti-inflammatory, anticancer, and contraceptive properties. By identifying secondary components of natural goods and medicinal plants, various advancements in conventional cancer treatments have been recorded. Anticancerous properties of plant emerge from their capacity to repress cancer-stimulating enzymes, advance the production of antitumor enzymes in cells, repair DNA, increase immunity and provide antioxidant effects. Plant-derived metabolites are the organic substances that are derived from plants (Sagar Satish Datir, 2018). Secondary metabolites (flavonoids, terpenoids, steroids, alkaloids) have the ability to inhibit carcinogenesis. The essential organic compounds are extracted from different parts of the plant like leaf, root, seed etc. They can initiate apoptosis by pathway of mitochondria through activation of caspase which causes development of apoptosis inducing factor (AIF). Secondary metabolites can also initiate production of caspase-3 and Bax which leads to inhibition of antiapoptotic factors. Some of them can lead to initiation of arrest of checkpoint of cell cycle at G1 phase, G2/M transition and G1/S transition by down regulating cyclin-D1 and upregulating P21. Some bioactive compounds can inhibit activity of COX-2, Insulin-like Growth Factor-(IGF-1) and Proliferating Cell Nuclear Antigen (PCNA). So, conventional drugs have been utilized to treat cancer due to their antioxidant nature, anti-invasive properties and anti-angiogenic properties (Esmeeta *et al.,* 2022; Saranya *et al.,* 2022). List of medicinal plants are reported having metabolite showed anti-colorectal cancerous effects (Fig. 3 a-o and Table 3).

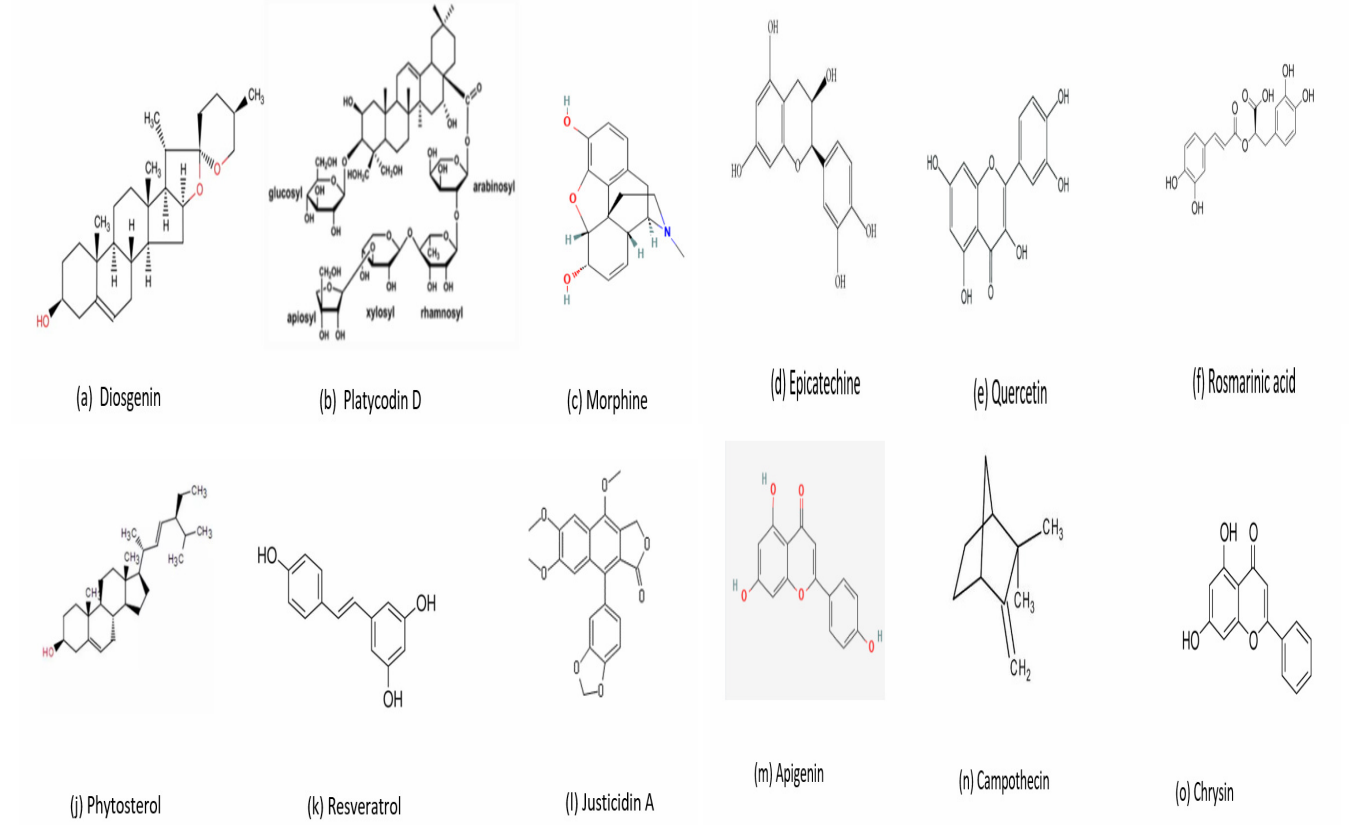


Fig. 3(a-o): Plant derived secondary metabolites

Anti-tumerous effects of plant derived metabolites (Diosgenin) in CRC through signaling pathway

Diosgenin (DSG), an important saponins, extracted from medicinal plant, play an important role in colorectal cancer treatment. Diosgenin (DSG) is important saponins, extracted from the fenugreek genera of plant kingdom. Previous studies showed that many plant derived metabolites showed pharmacological functions. DSG also showed many pharmacogenic properties like anti-oxidative, anti-inflammatory, hypolipidemic, anti-diabetic, anti-cancerious etc. DSG exerts anti-tumor activity in multiple cancers, including CRC. CRC as a fatal human tumor of intestine has been demonstrated that could be inhibited and induced to apoptotic by DSG. It has been reported that DSG is regulated by various signaling pathways, which are very important for carcinogenesis on numerous cancer cells in human body.

Table 3: Plant- derived metabolites used in the treatment of colorectal cancer

S. No.	Plant name	Plant part used	Anticancer agents	Activity	Reference
1	*Trigonella foenum graecum* (fenugreek)	Seeds, Roots	Diosgenin, dioscin, Quercitin	Inactivation of cAMP/PKA/ CREB signaling pathway	El Bairi *et al.,* 2017
2	*Platycodon grandiflorum* (Balloon flower)	Root	Platycodin D	Activate AMP- activated protein kinase leads to apoptosis, cell cycle arrest, autophagy	Jeon *et al.,* 2019
3	*Papaver somniferum* (opium poppy)	Latex	Morphine, narcotine, codeine	Fragmentation of DNA, inhibit NF-kB and KT-90	Afzali *et al.,* 2015
4	*Phaseolus vulgaris (*Common bean)	Seed	Epicatechine, Anthocyanin	reduces ROS production, COX-2 expression.	Ombra *et al.,* 2016
5	*Pisum sativum* (Pea)	Seed	Apigenin, kaempferol	Induce mitochondrial dependent apoptosis through Bax activation	Rungruangmaitree and Jiraungkoorskul, 2017
6	*Rosamarinus officinalis* (Rosemary)	Aerial parts	Carnosic acid, rosmarinic acid, rosmanol	Block angiogenic functions of endothelial cells and cytokine induced adhesion via NF- kB	Allegra *et al.,* 2020
7	*Trifolium pratens* (red clover) *e*	Flower	Formononetin	Inactivate ERK pathway, inhibit tumour growth in vivo	Ong *et al.,* 2019
8	*Vitex rotundifolia* (muscadine)	All parts	Camphene, diterpene	Down-regulation of cyclin D1 and CDK4 via transcriptional inhibition	Chaudhry *et al.,* 2019
9	*Capsicum annuum ((*Bell pepper *)*	Fruit	Luteolin	Induce cell apoptosis, suppress CREB 1 expression	Osman *et al.,* 2015
10	*Coix lachrymal jobi* (Job's tear)	Seed	Coixenolide, phytosterol	Suppress preneoplastic lesion of colon, COX-2 expression	Manosroi *et al.,* 2016
11	*Polygonum cuspidatum* (Japanese knotweed)	All parts	Resveratrol, Polydatin, emodin	Inhibit invasion and metastasis via MALAT 1 mediated Wnt/ β- Catenin signal pathway.	Wu *et al.,* 2018
12	*Justicia procumbens* (water willow)	All parts	Justicidin, diphyllin	Decrease level of cytosolic Ku 70 leading to apoptosis	Liu *et al.,* 2018
13	*Matricaria chamomilla (*Chamomile)	All parts	Apigenin	Inhibit Wnt/β-Catenin signal pathway.	Al-Dabbagh *et al.,* 2019
14	*Nothapodytes nimmomiana*	Bark	Camptothecin	Induce apoptosis and cell cycle arrest invitro and in vivo	Mithun *et al.,* 2017
15	*Passiflora caerulea* (Bluecrown Passionflower)	Flower	Chrysin	Induce autophagy by increasing reactive oxygen species (ROS) level.	León *et al.,* 2015

Lepage *et al.,* 2011 reported DSG regulate death receptor 4 through activation of p38 pathway to induced apoptosis in colon cancer. However, the approaching pathway of DSG, through which it suppresses CRC, remains further to be revealed. Li *et al.* (2021) reported inhibition of CRC cells proliferation in measurable quantity and time dependent way. DSG induced apoptosis via altering the p53 and Bcl-2 proteins expression in the direction of mediating mitochondrial apoptosis pathway, and concealed relocation and invasion through falling MMP-9 (matrix metallo-proteinase) and declined aerobic glycolysis by reconciling glucose transporter (*GluT 3 and GluT4*) and pyruvate carboxylase (Fig. 4). Interestingly, current studies showed that DSG inhibited cAMP/PKA/CREB pathway in CRC

cells, and result to inhibit the phosphorylation of CREB to regulate the transcription of genes. Finally, DSG is a shows potential drug use in the CRC treatment.

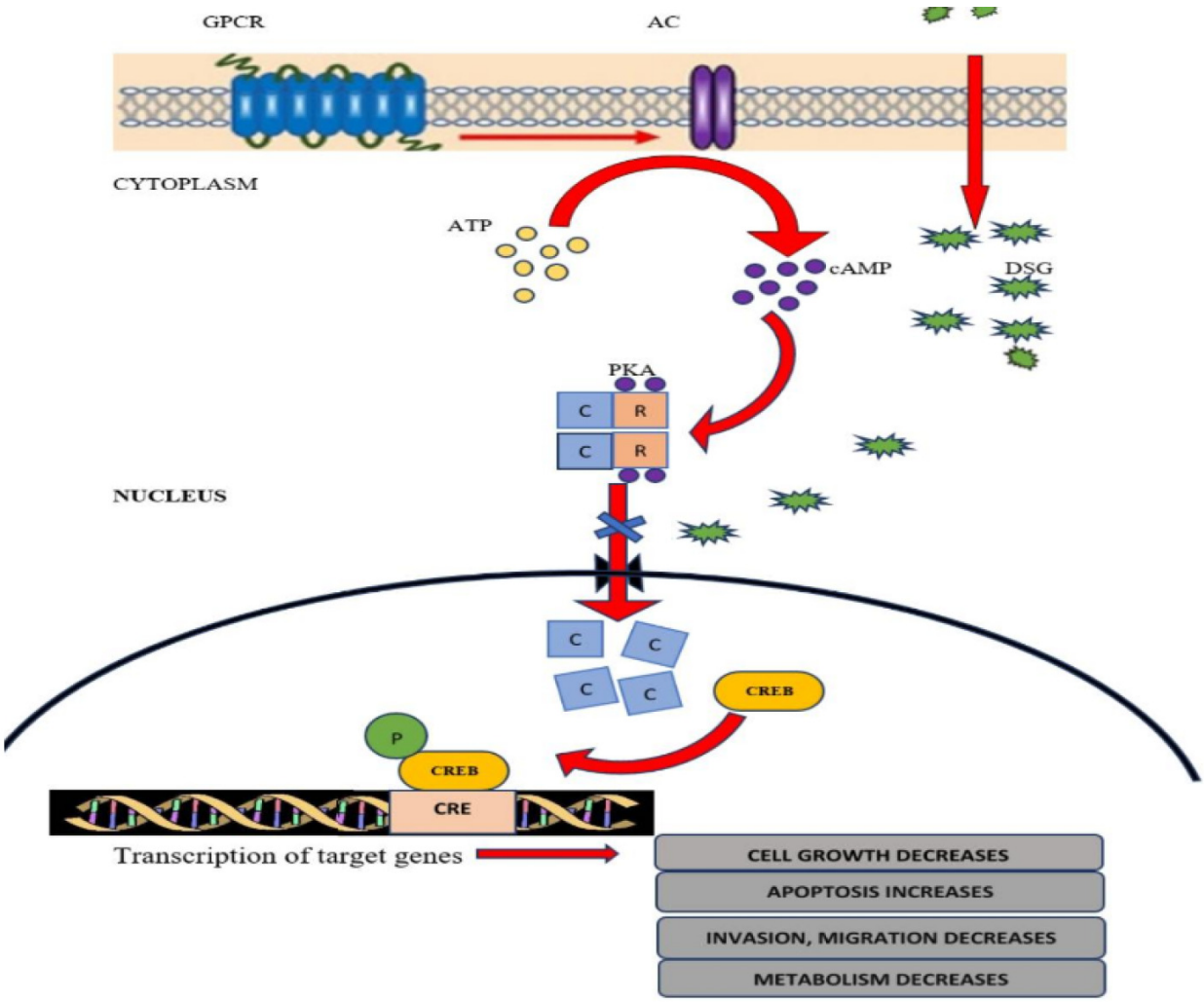


Fig. 4: Anti-tumerous effects of plant derived metabolites (Diosgening) in CRC through signalling pathway

Conclusion

Metabolites from plants have great promise for treating deadly conditions like cancer. The anti-cancer potential of several medicinal plants is now being researched. Cell culture methods and bioreactors can be used to generate or synthesize anticancer medicines or metabolites on a bigger scale. Several secondary metabolites like alkaloids, phenolics, flavonoids, saponins, terpenoids, quinones are described in this review to have anti-colorectal cancer capabilities against RKO, HT-29, T47D, SW1463, T84, in Caco-2, Colo 205, HCT-116 colorectal cancer cell lines. These have ability to block cancerous cell proliferation and activate caspase cascade to initiate apoptosis via different mechanism pathways. Even yet, there are several problems with investigating the most effective phytochemical substances for cancer treatment. It is a tough process which demands for more sophisticated technological and analytical techniques for determining potential chemicals, their bioavailability, and how they function on target tissues. Before approving any of these compounds for routine use in the management of colorectal cancer, there are still a number of issues that need to be resolved. However, more research should be conducted to identify and categorize the dose levels required to achieve adequate preventative therapy.

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