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Review Article

AN OVERVIEW OF COLORECTAL CANCER: IMPLICATION OF TWO MEDICINAL PLANTS IN THEIR TREATMENT

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ABSTRACT

Nowadays, cancer is one of the most common diseases in humans. Among all types, colorectal cancer (CRC) is one of the most serious types diagnosed in men after lung and prostate cancer while in women it occupies the second position after breast cancer worldwide. The risk factors such as obesity, sedentary lifestyle, bad nutritional habits (high in fats and proteins), smoking, and progressive aging are the cause of CRC. The acquisition of abnormal mutations leads to a consisting of many different arrangements of events during the tumor development process. Over the years, different approaches have been employed, in the treatment of cancer. These include chemotherapy, radiotherapy, surgery, and immunotherapy. Chemotherapy is routinely used for cancer treatment, but the toxicity of chemotherapeutics on healthy cells of the human body is obvious. This is the reason for discovering the new, natural origin, substances with potential cytostatic effects and less toxic side effects on the healthy cells. Medicinal plants have a special place in the management of cancer. Numerous cancer research studies have been conducted using traditional medicinal plants to discover new therapeutic agents with fewer side effects. In this review, we are describing two medicinal plants such as *Actiniopteris radiata* (Sw.) Link (Mayurashikha) and *Terminalia pallida* Brandis (Tella karaka) (endemic plant) which are available immensely in Chittoor District are used till today by the traditional herbal practitioners, tribal people is near to Talakona forest and Ayurvedic people for various diseases and also for CRC.

Keywords: Colorectal cancer, Risk factors, Pathogenesis, Treatment, Medicinal plants

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INTRODUCTION

Colorectal cancer (CRC) is the fourth most common type of cancer in the world, with 1.3 million new cases each year and a 5-year prevalence rate of 3.2 million cases [1,2]. In 2012, there were an estimated 693,333 deaths due to CRC. The prevalence of CRC is higher in developed countries than in developing and undeveloped nations. Adults greater than 50 years are more prone to be affected by CRC, and incidence in males is greater than in females [3]. The CRC incidence and percentage vary from one place to another place in all over the world. In India, the incidence is higher in males; it is the fifth most common cancer following breast, cervix/uteri, lip/oral cavity, and lung cancer [1].

CRC is cancer that starts in either colon or rectum. It usually starts as a polyp in the intestinal mucosa exists as an initial benign lesion called adenoma that can transform into a malignant lesion depending on its histological presentation, and its size, of which 60% of cases are simple adenoma, and 40% are multiple adenomas. About 24% of patients with untreated polyps will develop cancer [4].

The clinical presentation of CRC depends on the location, size, as well as the presence or absence of metastasis. The symptoms include abdominal pain, alteration of chronic bowel habits, changes in bowel movements, involuntary weight loss, nausea, vomiting, malaise, anorexia, and abdominal distension [5]. Distal cancers cause evident rectal bleeding in comparison to proximal cancer that can give mixed blood with stool, so it tends to occulted, and in consequence, anemia may be presented as a secondary sign.

RISK FACTORS

The risk factors responsible for CRC are diet and westernized lifestyle; there is no specific food or another environmental agent that has been identified as an exact causative factor [6].

CRC identified types are hereditary nonpolyposis, familial adenomatous polyposis, inflammatory bowel diseases [7-10], human papillomaviruses, and acquired immunodeficiency syndrome [11]. Approximately 20% of CRC cases are associated with familial clustering, and patients with colorectal adenomas or invasive CRC are at increased risk for CRC [12-15].

The different lifestyle factors are associated with development of CRC including high alcohol consumption (60%) [16], high-fat diet poor in fiber, red meat, obesity, smoking (20%), lack of physical exercise [17], diabetes [18], older age, and family history (20%) [19].

STAGES OF COLORECTAL CANCER

CRC is classified under the Astler-Coller-Dukes system or tumor, node, and metastasis system established by the American Joint Committee on Cancer [20], which represents the stages of CRC by categories. The letter T represents the spread of tumors through the layers of the colonic or rectal wall, the letter N indicates if there is the propagation of tumors in the lymph node, and M indicates metastasis to distant organs [21]. The T, N, and M scores are combined to assign the CRC stages. There are five stages and they are numbered like I (1), II (2), III (3), or IV (4) (Table 1).

PATHOGENESIS

The bases of CRC hallmarks are genomic instability and inflammation. Genomic instability confers random mutations including chromosomal rearrangements, mutation errors in DNA, genes involved in the control of the cellular cycle, repair, and apoptosis or mutations in tumor suppressor gene such as adenomatous polyposis coli (APC), deleted in CRC (DCC), B-Raf proto-oncogene (BRAF), phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), protein kinase B, and tumor protein (TP53) or the presence oncogenes as Kirsten rat sarcoma (K-ras), and Catenin Beta 1, while the inflammatory state of premalignant and malignant lesions that are driven by cells of the immune system also fosters multiple hallmark functions [3].

Fearon and Vogelstein hypothesized that colorectal carcinogenesis is a multistep process in which genes are mutated in a specific order [22], resulting in the transition from normal mucosa to benign adenoma to severe dysplasia to carcinoma. The first in this process is the loss of APC tumor suppressor gene, which results in loss of DCC gene and activation of K-ras oncogene. This is followed by the inactivation of p53, leading to eventual carcinoma formation. This is in agreement with Knudson's two-hit theory in which the carcinogenesis process is thought to result from an accumulation of two or more mutations that affect cell cycle control aberrations or other features of neoplastic development [23].

- First, the inactivation or alteration of the APC gene, i.e., tumor suppressor gene can lead to the activation of the Wingless-type pathway, a common mechanism for initiating polyp to cancer progression sequence [24]
- Second, mutations of oncogenes, K-ras virus oncogene homolog or B-Raf proto-oncogene, aberrantly activating the mitogen-activated protein kinase signaling pathway leads to increase cell proliferation [25,26]
- Third, the inactivation of the DCC gene is a late event in the carcinogenesis of CRC and has a role in metastasis [27]
- Lastly, P^{53} is a tumor suppressor (transcriptional factor) that controls the cell cycle, apoptosis, and DNA repair mechanisms [28]. Hence, P53 mutations or the loss of its functionality and the frequency of alterations in the gene increases with the corresponding progression of the lesion [29].

Finally, the inflammatory proteins such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and Cyclin D1 over expression lead to colorectal carcinogenesis

DIAGNOSIS

Current screening methods are targeted toward moderate risk population aged 50 or more [32].

- Medical history: The causes of CRC are unknown. By collecting the medical history of a patient include disease conditions/and certain medications, long-term usage lead to CRC will help to predict the causes of CRC
  - Example: (a) Lynch syndrome also called hereditary non-polyposis colon cancer is an inherited syndrome and familial adenomatous polyposis is a rare inherited syndrome that often leads to CRC
- Physical exam: Along with taking medical history, it is also important to examine the patient's physical parameters to know about functions for the sign of disease
  - Example: Body temperature, blood pressure, pulse rate, and respiration rate

Table 1: Tumor, node, and metastasis classification and stages of colorectal cancer

AICC stage	TNM stage	TNM stage criteria for colorectal cancer	
Stage I	T1 N0 M0	T1	Tumor invades submucosa
Stage I	T2 N0 M0	T2	Tumor invades muscularis mucosa
Stage II-A	T3 N0 M0	T3	Tumor invades subserosa or beyond
Stage II-B	T4 N0 M0	T4	Tumor invades adjacent organs or perforates the visceral peritoneum
Stage III-A	T1-2 N1 M0	N1	Metastasis to 1 to 3 regional lymph nodes. T1 or T2
Stage III-B	T3-4 N1 M0	N1	Metastasis to 1 to 3 regional lymph nodes. T3 or T4
Stage III-C	Any T, N2 M0	N2	Metastasis to 4 or more regional lymph nodes. Any T
Stage IV	Any T, any N, M1	M1	Distant metastases present. Any T, any N

TNM: Tumor, node, and metastasis

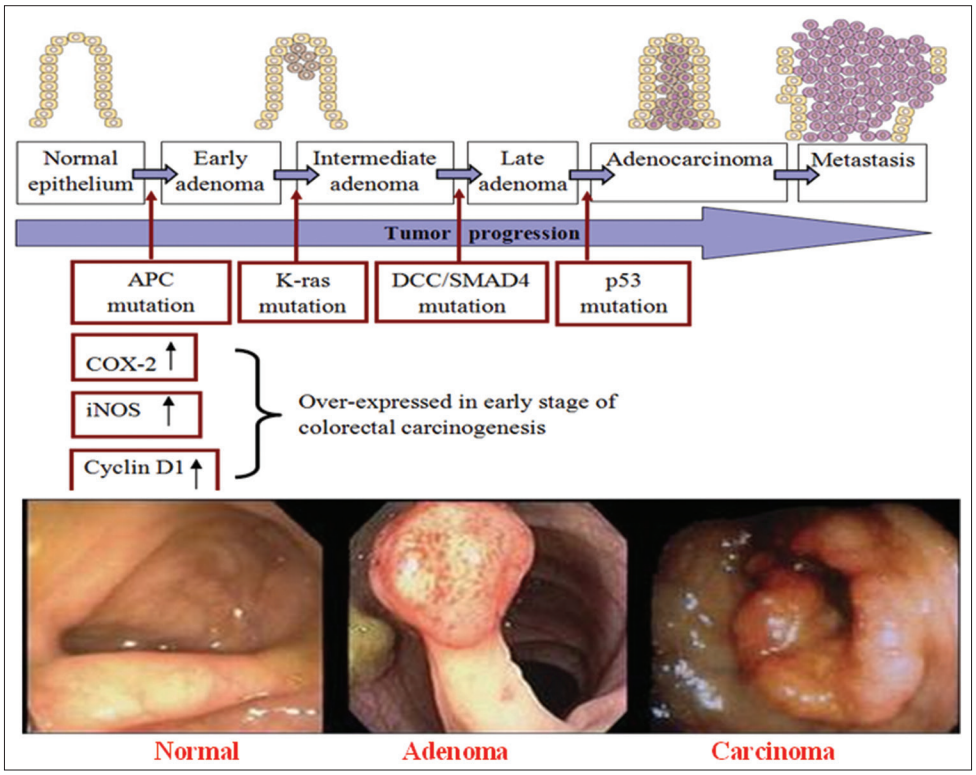

Fig. 1: Colorectal cancer is a multi-step process in which genes are mutated in a specific sequence [30,31]

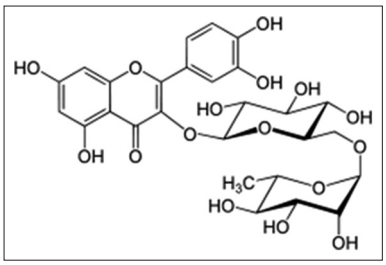

Fig. 2: Structure of Rutin-flavonoid glycoside (quercetin-3-rutinoside)

Fig. 3: *Actiniopteris radiata* (Sw.) Link (Mayurashikha)

Fig. 4: *Terminalia pallida* Brandis (Tella karaka) (Endemic plant)

- Total colonoscopy: It is a procedure in which the morphology of large intestine can be examined. This study helps in finding out the growth of polyps and any other disease related to the colon
- Blood tests: These are used to evaluate the disease by estimating biochemical parameters. (i) Complete blood count measures the number of blood cells in a sample and (ii) chemistry profile-CRC spreads cause high or low levels of chemicals in the blood
  - Example: High carcinoembryonic antigen level
- Imaging tests: (i) Computerized tomography (CT) with contrast–CT takes many pictures a body part using X-rays, (ii) magnetic resonance image–uses a magnetic field and radio waves to take pictures, and (iii) positron emission tomography/CT-scan can show tumor size and also can find whether a tumor is a metastasis or not
- Needle biopsy: Samples of tissue or fluid removed from the body with a needle sent to a pathologist for cancer testing by performing the RAS mutation test, v-Raf murine sarcoma viral oncogene homolog B mutation test, and mismatch repair protein (MMR), or microsatellite instability test
- Immunochemistry panel is used to assess MMR proteins.

TREATMENT

The treatment for CRC depends on whether the disease is nonmetastasis or metastasis. The mainstay curative treatment for patients with nonmetastasized tumors is surgery. However, the outcome is strongly related to the quality of surgery [33,34] the quality of preoperative staging and treatment selection. Local recurrences after the colon and rectal surgery can be minimized using short-course radiotherapy [35-37], although long-term therapy showed no effect on overall survival for this approach [38]. Neoadjuvant radiotherapy/chemoradiotherapy) can be proposed for patients with unfavorable T3 rectal tumors. The chemotherapy backbone for first-line treatment of metastatic disease is typically a combination of leucovorin, 5-fluorouracil, and either oxaliplatin or irinotecan (Adjuvant chemotherapy) [39]. Some of the researchers have focused on this adjuvant chemotherapy drugs to overcome therapy resistance, reduce dose requirements, drug-induced adverse effects and increase cytotoxic effects using histone deacetylase inhibitors (Vorinostat, romidepsin, panobinostat, and belinostat) [40]. These treatment methods are not as effective in treating cancer cases in the metastasis stage. Cancer treatment failure, through chemotherapy, can happen because of the low selectivity of the cytotoxic and uncertainty of the molecular targeted [41]. Chemotherapy can put the patient under a lot of strain and further damage their health. Hence, many of the researchers have to focus on using alternative therapies against cancer with low side effects.

Nowadays, the most important problem in cancer treatment is destroying tumor cells in the presence of natural cells, without damaging natural cells. To prepare anticancer medicines from natural resources such as plants, testing cytotoxic compounds, and screening raw extracts of plants are necessary [42]. Therefore, the availability of natural products with higher effectiveness and lower side effects is desired [43]. Medicinal herbs are important for cancer treatment due to their multiple chemical compounds for discovering new active materials against cancer [44]. These compounds are called secondary metabolites. Alkaloids, terpenoids, flavonoids, pigments, and tannins are important constituents of these compounds. Secondary metabolites have biologic effects such as anti-inflammatory, anticancer, contraceptive, and different effects on hematopoietic cells [45], lipids [46], and cardiovascular systems [47]. Different improvements are reported in common treatments of cancer by finding secondary compounds of natural products and medicinal herbs. It is believed that anticancer effects of plants develop by suppressing cancer's stimulating enzymes, repairing DNA, stimulating the production of antitumor enzymes in the cell, increasing body immunity, and inducing antioxidant effects [48,49].

The different researches and studies have been proved the positive effect of plants in curing diabetes, fertility, and sterility, thyroid disorders, anemia, psychological disorder, etc. Finding plants that replace chemotherapy and cumbersome cures of cancer with cytotoxic effects are necessary.

In this review, we chose *Actiniopteris radiata* and *Terminalia pallida* ayurvedic plants to describe the mechanism of action for the treatment of CRC. Mayurashikha (*A. radiata*) is an ayurvedic herb and a tiny terrestrial fern found throughout India. It is also called as Peacock's tail. *A. radiata* (Sw.) Link. belonging to the family Polypodiaceae. It is also found in different places such as Burma, Sri Lanka, Afghanistan, Persia, Arabia, Yemen, South Eastern Egypt, Tropical Africa, Australia, and Madagascar. The whole part of the plant is used in wounds, intestinal worms as a cooling agent in syphilis, rickettsiae, piles, leukorrhea, typhoid [50], cough, high blood pressure, tuberculosis, asthma, fever, leprosy, and hair growth [51]. The leaves of the plant are used for aphrodisiac [52], to increase the potency in women [52-54], as leukorrhea, as fertility [55,56], in irregular menstrual period, for conception, and birth control [51]. The stem of this plant is used in diarrhea [56,57].

The chemical constituents such as flavonoid glycoside (Quercetin-3-rutinoside), steroidal compounds (β-sitosterol, β-sitosterol palmitate, and β-sitosterol-D-glucoside), alkane hydrocarbon chains (hentriacontane and hentriacontanol) [58], and glycosides (2-(3, 4-O–diglucos cinnamoyl)– 4– hydroxyl furan and 1-Heptaloyl, 8-hexyl, 3-(O–diglucos), 10–methyl, 9, 10–dihydro naphthalene) are used [59]. The other constituents are glucose, fructose, flavonoids, alkaloids, tannins, phenols, saponins, quinines, terpenoids, coumarins, β-cyanin, and triterpenoids [60].

The plant extract possesses different research activities such as analgesic activity [61], antihistaminic and anti-cholinergic activity [62], antifertility [63], antitubercular [64], antibacterial [65], anthelmintic [66], antifungal [67], wound healing [61], antistress and antiallergic effects [68], antioxidant and radical scavenging activity [69,70], hepatoprotective activity [71] diuretic, anti-inflammatory, and antidiabetic activity [72]

T. pallida Brandis is herb from the family Combretaceae. It is a semi-evergreen tree group. Leaf fall and flushing events occur during the pre-monsoon season; leaf flushing extends into the monsoon season. The flowers are bisexual and obligately outcrossed and enforced by self-incompatibility. Fruits fall to the ground when mature and dry in the presence of wind. The fallen fruits are scattered by rainwater, and the seeds germinate and establish seedlings depending on the soil status [73]. It is one of the oldest medicinal herbs of India, which is an ingredient of Indian Ayurvedic drug "Triphala" used for the treatment of digestion and liver disorders. In Indian traditional system of medicine, the fruits are also used in the treatment of hepatic disorders and the treatment of diabetes by tribal people [74]. The leaf is used for treating skin blisters and skin diseases, whereas the stem bark is used as a diuretic and for swellings. The fruit is used as an anti-pyretic, purgative, for diarrhea, peptic ulcers, diabetes, venereal diseases, cough, cold, dysentery, fissures, and cracks; and in tanning and dying. Bark powder is applied externally and can be taken internally as an anti-inflammatory agent. Fruit powder is given orally to cure peptic ulcer fissure and to clear the harshness of voice [75-77].

The reported biological activities of *Terminalia pallida* such as anti-oxidant activity and hepatoprotective potential [78], analgesic and anti-pyretic activity [75], anti-diabetic activity [76], anti-atherogenic and anti-hyperlipidemic activities of fruits [77], anti-ulcer activity [79], anti-bacterial activity [80], phytochemical evaluation and antimicrobial studies [81]. This plant has many important phytoconstituents such as gallotannic acid, bellericanin, gallic acid, ellagic acid, termilignan, thannin lignin, flavones and anolignan B, tannins, ethyl gallate, ellagic acid, gallonyl glucose, and chebulagic acid, phenyllemblin, beta-sitosterol, mannitol, rhamnose, and glucose [75-77,79,81]

Medicinal plants are representing a wide variety of phytochemicals with pharmaceutical potential such as phenolic acids, flavonoids, steroids, terpenoids, and triterpenoids. Polyphenols such as flavonoids and phenolic acids have been reported to have many pharmacological activities, such as antioxidant, anti-inflammatory, anticarcinogenic, antiviral, or anti-allergic effects [82-86]. Among anticancer and cancer-preventing drugs, flavonoids are the most studied ones. These compounds can interfere with specific stages of the carcinogenic process, inhibit cell proliferation, and induce apoptosis in several types of cancer cells [87-91]. Flavonoids exhibit a good antioxidant activity by inhibiting reactive oxygen species generation/affecting the activity of sundry detoxifying enzymes, such as COXs, Lipoxygenases, and iNOS [92-94]. This antioxidant capacity of flavonoids could possibly account for their anticancer potency. Flavonoids have also been found to influence epigenetic alterations by chromatin remodeling [95,96]. Hashemzaei *et al*., 2017 [81], were reported and proved that quercetin (belongs to polyphenolic flavonoid) is a potent anticancer agent in *in vitro* and *in vivo* cancer studies. In particular, it has been reported that quercetin at various concentrations, suppresses tumor growth of various cancer cell lines, including breast, colorectal, stomach, head and neck, lung, ovarian, melanoma, and leukemia [97-107]. Mayurashikha contains major phytoconstituent is rutin (Quercetin-3-glycoside) [58] and *T. pallida* with a major constituent is phenolic acids [81]. Due to the presence of phytoconstituents, in these plants may show the antioxidant and anticancer property that happens maybe by inducing apoptosis initiation, ATP-dependent chromatin remodeling, reduce COX-2 overexpression and DNA methylation, histone modification, inhibition of misregulation of miRNA, and tumor angiogenesis and also can modify the different cellular signaling pathways involved in cell proliferation.

The above two medicinal plants will be the plan to do research work for anti-CRC activity *in vitro* and *in vivo* cancer models.

CONCLUSION

CRC is a leading problem globally, especially in developing countries and also in developed countries because many of the people migrated from village to town; changing their lifestyles and food habits. Majority food intake and lifestyle habits are the risk factors for the development of cancer in the colon. Management of CRC by surgery followed adjuvant therapy (Radiotherapy and chemotherapy) produce high toxic effects which can be minimized with supplementation of medicinal plants (Ayurveda). Medicinal plants have a major role in the treatment of different ailments like cancer because they have major nutritive values and antioxidant properties. Mayurashikha (*A. radiata*) and *T. pallida* Brandis are two medicinal plants with specific active constituents that may show anti-CRC property.

AUTHORS' CONTRIBUTIONS

Jyothi Basini, Sireesha Rayadurgam, and Swetha Dakshinamurthy have contributed for review article preparation and editing of the manuscript.

COMPETING INTERESTS

The authors declare that there are no conflicts of interest.

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