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REVIEW ARTICLE

Colorectal Cancer Management and Prevention Using Plant Polyphenols in the Rodent Models

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ABSTRACT

Colorectal cancer is among the most common and deadliest types of cancers affecting humans and animals. Currently, chemotherapeutic and radiotherapeutic measures are being practiced in treating it but they have devastating side effects including cardiopathologies and nephropathologies. Moreover, they are unreliable and can not provide complete treatment in advanced cases. These scenarios necessitate therapeutic substances for the prevention and treatment of colorectal cancer. Plant-based compounds, especially various types of phenolics are among the most considered substances as alternatives to prevent and treat colorectal cancer. Among all the phenolics, multiple compounds belonging to flavonoids, flavone, flavonol, and stilbenes have been found effective in treating and preventing colorectal cancer. Predisposing factors that lead to the development of colorectal cancer depend upon living type, feeding type, genotype, age, gender, and exposure to carcinogens. All the polyphenolics prevent colorectal cancer by detoxifying carcinogens, oxidative stress management, reduction in preneoplastic lesions. Specifically, quercetin can arrest S, G1/S, and other stages of cancerous cells, resveratrol controls cancerous cell proliferation and detoxifies the pathological effects of anticancer therapeutic agents by regulating several enzyme systems, and kaempferols control aging process, and uncontrolled metastasis by regulating relevant enzyme systems. All these polyphenolics arrest cancer metastasis by limiting abnormal cell division, preventing extracellular skeletal system damage, and several other pathways. Additionally, they have been found safe for all the systems of the body which is their advantage over current cancer therapies. All of these have passed *in vitro* trials and proven effective. Currently, xenograft rodent models are being used and these *in vivo* models also approve their therapeutic use of some polyphenolics i.e., resveratrol and kaempferol are being clinically used as synergists to chemotherapeutic substances. This review highlights the potential of selected polyphenolics as preventive and cancer-treating substances in the light of *in vivo* studies in rodent models.

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INTRODUCTION

Colorectal cancer is among the most common types of cancer and is the third most common cancer among all types of cancers (Lewandowska *et al.*, 2022; Siegel *et al.*, 2023). This is the second deadliest cancer found globally among all types of cancers (Xi and Xu, 2021). Colorectal cancer is abnormal neoplastic growth containing undifferentiated cells in the colon-rectal region of the large intestine (Tirendi *et al.*, 2023). It is a point of note that colorectal cancer should not be confused with colon cancer because it has significant differences from the cancer of the colon (upper/right side) based on etiology, oncology, and pathology (Banerjee *et al.*, 2021). There may be multiple reasons for the development of colorectal cancer, and these may be genetic and acquired reasons (Lewandowska *et al.*, 2022). Primary signs include pain in the lower abdominal area or lower part of the intestine, blood before or after the defecation, severe constipation, rapid decrease in weight, abnormal intestinal movements,

and continued fatigue (Low *et al.*, 2020; Siegel *et al.*, 2020). These are among the basic signs and in most cases, there are no diagnosable signs and only the metastasis phase is diagnosed. The World Health Organization has threatened that if early diagnostic, preventive, and treatment strategies are not adopted then colorectal cancer may cause more than three million annual cases with 50% of deaths of cancer-containing people by 2040 (Morgan *et al.*, 2023). The colorectal cancer is mostly spread in the high income countries across the globe as per the world cancer research fund report based on the data 2022 (Table 1).

Research is being done on prevention and therapeutic strategies to avoid any alarming situation shortly. The treatment strategies being opted for the treatment of colorectal cancer include chemotherapy, radiotherapy, immunotherapy, and biological therapies (Birrer *et al.*, 2021; Osei-Bordom *et al.*, 2021). Chemotherapy and radiotherapy focus on curing cancer by destroying the tumor cells using chemical substances and radiation respectively (Mathan *et al.*, 2022). These are the most practiced strategies for the treatment of any type of cancer including colorectal cancer (Shaukat and Levin, 2022). Chemical substances and the radioactive methods of treatment are potent for controlling cancerous cell growth, proliferation, and metastasis i.e., crossing the barriers (Steeg, 2021). These therapies are being practiced but have never been ideal for researchers to use because of multiple side effects and the costs of the treatment.

Radiotherapy is the most used technique for the treatment of cancer, but it is devastating for the cells and tissues of various organ systems (Saini *et al.*, 2020; Wang and Tepper, 2021). Abnormal exposure to radiotherapies may lead to multiple pathologies including the risk of developing another type of cancer (Barazzuol *et al.*, 2020; Wei and Cheng, 2021). Commonly reported side effects of radiotherapy include cardiopathies, alopecia, skin damage, eyesight disturbance, nausea, anorexia, and blood cell destruction (Latoch *et al.*, 2022; Rukmi and Nofiyanto, 2023). Similarly, anticancer chemotherapeutic agents have several issues of similar types including effects on the renal systems, blood, and bone marrow abnormalities, immunosuppression, permanent loss of fertility, etc. (Schneider *et al.*, 2021; Mustapha *et al.*, 2022). These therapies put the patient in constant pain, irritation, emaciation, and multiple other associated risks and side effects (Yazbeck *et al.*, 2022). Immunotherapies are being used but only as assisting strategies especially at proliferative strategies but not at initial stages (Martin *et al.*, 2020).

The situation of colorectal cancer is demanding the focus of scientists to develop strategies for the prevention and treatment of this disease (Hossain *et al.*, 2022). Scientists are focusing on combined strategies to control colorectal cancer at its early stages and manage it potentially at the advanced stages (Siegel *et al.*, 2020; Shaukat and Levin, 2022). Multiple substances including peptides, vaccines, and phytochemical substances are being suggested that can be used as preventive and therapeutic substances for colorectal cancer (Das *et al.*, 2022). Among all these substances, phytochemicals possess special importance as preventive and chemotherapeutic agents for the management of cancers including colorectal cancer (Zhu *et al.*, 2020; George *et al.*, 2021). Multiple groups of plant-based compounds have been found effective in treating colorectal cancer including phenolics and their subclasses, terpenes and their subclasses, etc. (George *et al.*, 2021; Ayaz *et al.*, 2022; Islam *et al.*, 2022). Polyphenols are also among the most studied class of compounds that can be used in the future for the treatment of colorectal cancer (Hazafa *et al.*, 2020). Polyphenols have been studied in various *in vitro* and *in vivo* models and found to be a promising candidate to be studied for therapeutic and preventive substances in colorectal cancer (Bracci *et al.*, 2021; Stromsnes *et al.*, 2021). Although all the models have their importance, they can provide sufficient information but animal models, especially rodents, have special importance for the analysis of therapeutic effects of anticancer substances.

Animals, especially rodents, are among the most studied animals in biomedical research, and they are among the most reliable sources for toxicity and therapeutic analysis (Singh and Seed, 2021; Mukherjee *et al.*, 2022). Moreover, colorectal cancer is widely present in multiple pets including dogs and cats and the importance of treating these animals is also increasing, so there is a dire need to study and evaluate the studies in the animal models (Uneyama *et al.*, 2021). Xenografting is gaining popularity among scientists and rodents are the most convenient animals to be xenografted, so the rodent model poses a critical importance in cancer studies especially in colorectal cancer (Delgado-Roche *et al.*, 2020; Yusuf *et al.*, 2022; Arsul, 2023; De *et al.*, 2023). This review intends to analyze the potential of polyphenolics in rodent models; whether natural or xenografted; and their potential to be used as possible preventive substances in veterinary and human clinical aspects.

Table 1: Top 10 countries across the globe with gender-wise epidemiology of colorectal cancer in 2022.

Sr. No	Country/Region	Colorectal cancer cases (Million individuals)		
		Total	Male	Female
1.	China	0.517	0.307	0.21
2.	United States of America	0.16	0.8	0.8
3.	Japan	0.145	0.08	0.065
4.	Russia	0.83	0.039	0.044
5.	India	0.07	0.043	0.027
6.	Germany	0.063	0.033	0.03
7.	Brazil	0.06	0.032	0.0248
8.	Italy	0.055	0.029	0.026
9.	France	0.052	0.027	0.025
10.	United Kingdom	0.049	0.027	0.022

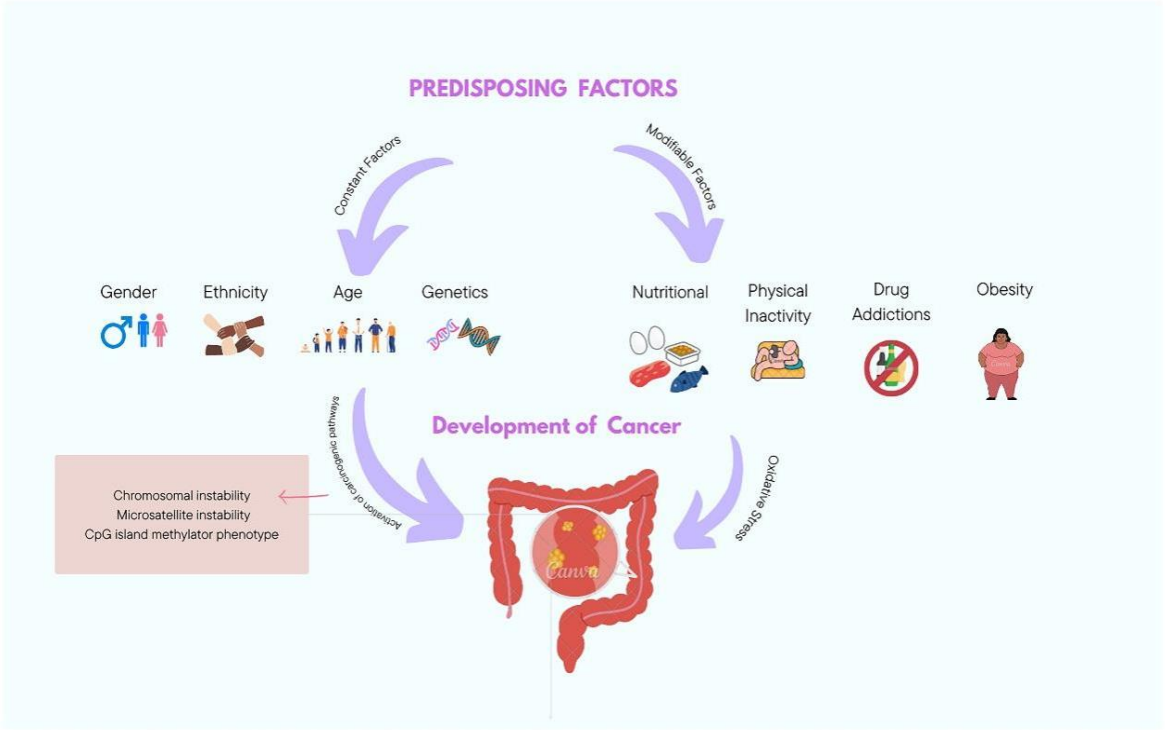

Fig. 1: Predisposing factors of colorectal cancer development.

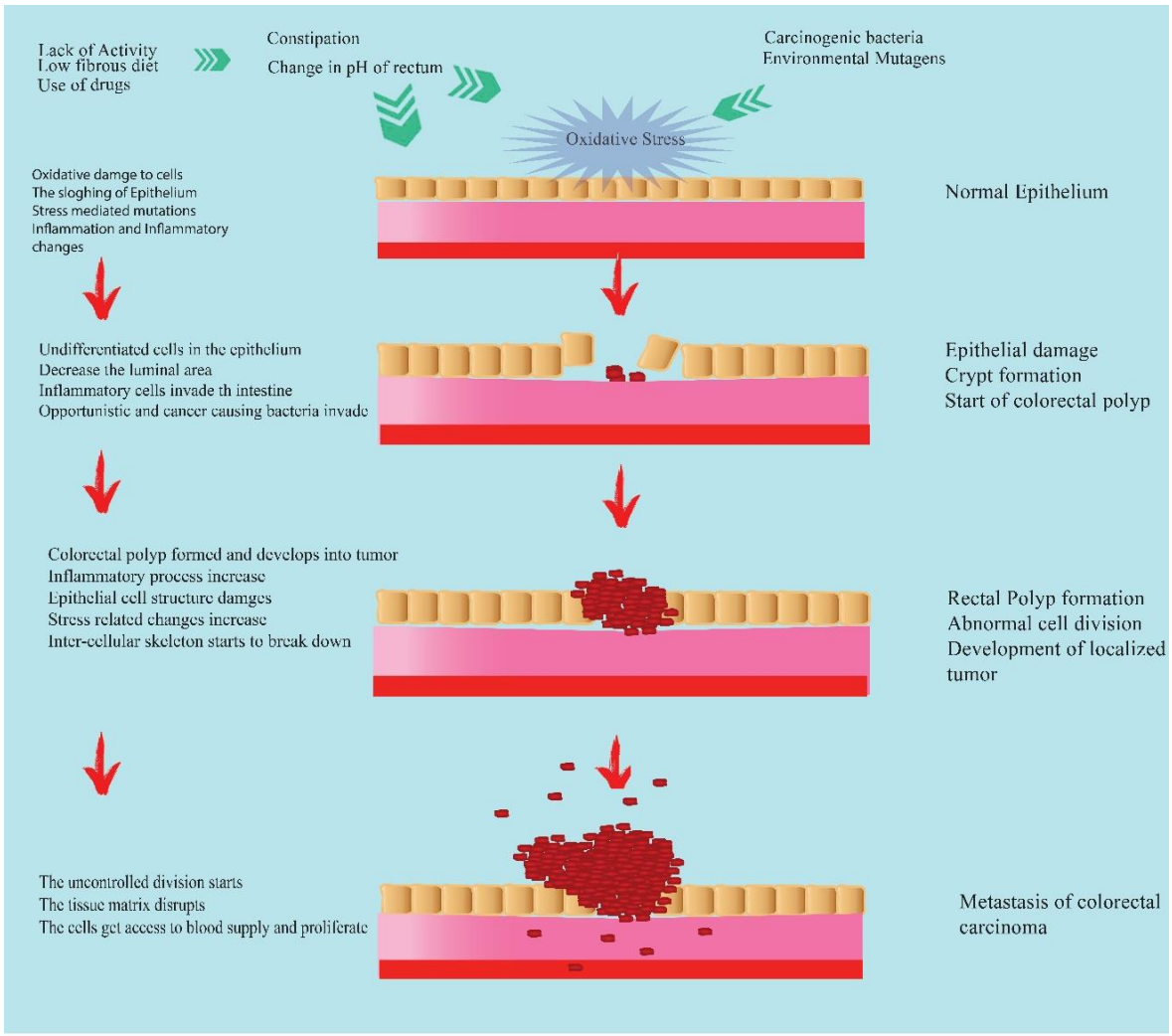

Fig. 2: Pathologies at various stages of colorectal cancer.

Table 2: Selected polyphenolic compounds for the treatment of colorectal cancer in rodent models.

Sr. No	Compounds	Class	Method of cancer inductions	Mechanism of actions	Type of animals used	Doses	Results	References
1	Quercetin	Flavonol	Azoxymethane in saline solution	Tumor suppression and reduction in gut microbiota reduced inflammatory markers and reduced reactive species leading to oxidative stress	Fischer-344 rats (male)	25 mg/kg	Reduction in the number of tumors, decrease in the colonies of tumor-related bacteria	(Pérez-Valero *et al.*, 2024)
2	Luteolin	Flavone				25 mg/kg		
3	Quercetin	Flavonol	CT26 tumor cell injection	Shown antitumor activity by suppression of heat shock proteins, especially heat shock protein 70 within the cancerous mass	BALB/c mice (Female)	50 mg/kg	Heat tolerance of the tumor was decreased, and the growth of the tumor was controlled by thermal therapy	(He *et al.*, 2013)
4	Resveratrol	Stilbenoid	Trypsin injection in the surgically exposed colon followed	Effected mir-96 target	$APC^{CKO}/Kras^{mu}$	150 and 300 ppm	Inhibited the tumor growth, and proliferation in the mice	(Saud *et al.*, 2014)
			CT26 and HCT116 cancerous cells were injected	Sensitization of cancerous cells by inhibition of AKT pathways	Balb/c females and nu/nu nude mice	1 mg/kg	Inhibition of the	(Wang *et al.*, 2020a)
5	Pterostilbene (Resveratrol derivative)		Azoxymethane induced cancer	DNA repair pathways (Top1/Tdp1-Mediated Pathway)	ICR mice	50 and 250 ppm	Controlled cancer by apoptosis induction and cell-cycle arrest	(Chiou *et al.*, 2010)
6	Kaempferol	Flavonol	Mice carry colorectal cancer through genetic modification	Downregulation of antigen Ki67 and leucine-rich G-protein receptor 5	ApcMin/+ Mice	50 and 100 mg/kg	Reduced colorectal tumor burden and restored the intestinal barrier affected by metastatic cells	(Li *et al.*, 2022)
			1,2 dimethyl hydrazine injection	Effected the peroxidation of fats and improved the antioxidant status	Wistar rats (Male)	10, 100 and 200 mg/kg	Improved the antioxidant levels and maintained the tumor levels	(Nirmala and Ramanathan, 2011)
			CCA cells injected in the tail vein	Inhibited the peptides dependent on zinc (MMP2, and MMP 9) that is responsible for metastasis of cancerous cells	BALB/c nude mouse (male)		Metastasis of the colorectal cancer was reduced in the lungs, induced apoptosis of cancerous cells	
7	Curcumin	Diarylheptanoid	CC531 cells injection		WAG/RiJHsd Rats	200 mg/kg	Decreased the hepatic proliferation and metastatic potential	(Herrero de la Parte *et al.*, 2021)

Predisposing factors of colorectal cancer: Prevention of colorectal cancer chiefly depends upon the predisposing factors and treatment depends upon the management of pathologies resulting from the cancer (Lewandowska *et al.*, 2022). Colorectal cancer has genetic and non-genetic factors (Fig. 1) which account for the activation of various pathways for the cancer development. Genetic factors account for 20% of total colorectal cancers while all the other factors account for 80% of the total types of cancer. (Baidoun *et al.*, 2021) Along with genetic reasons, some factors are unmodifiable factors to cause colorectal cancer (Hossain *et al.*, 2022). These include aging, gender, ethnic association, and multiple syndromes. These factors of colorectal cancer cannot be prevented; however, multiple other factors can be prevented (Sangamithra, 2021). Among all the other factors, nutritional factors are the most frequently associated with colorectal cancer and reports suggest that changing nutritional factors may

reduce up to 70% risk of acquired colorectal cancer (Kanth and Inadomi, 2021). Smoking and drinking also enhance the risk of colorectal cancer. Physical inactivity, obesity, and exposure to carcinogenic substances along with some types of bacteria are among the most prominent factors associated with colorectal cancer (Vacante *et al.*, 2020) (Fig. 1).

Above mentioned factors are associated with the initiation of colorectal cancer. Most of the time (estimated 80%) neoplastic polyps in colorectal regions develop into cancerous masses and metastasize (Shaukat *et al.*, 2020). These polyps are slow-developing chronic masses and may take 40-50 years to develop into cancerous polyps (Vacante *et al.*, 2020). These factors lead to the development of colorectal preneoplastic adenomas which further grow into granulomatous masses and if left undiagnosed they can metastasize and proliferate in the multiple organ systems of the body (Hossain *et al.*, 2022). Control of cancer before its proliferation is necessary.

The colorectal cancer can be categorized into various stages and the pathological advancements can be subdivided into some simple stages (Fig. 2)

Important polyphenols and their role in colorectal cancer management

Quercetin: Quercetin is among the most commonly prevalent polyphenolics in nature (Ulusoy and Sanlier, 2020; Bernini and Velotti, 2021). It's found in several vegetables, fruits, and other parts. It belongs to the flavanol subclass of flavonoids. Quercetin is a popular medical phytochemical under consideration for the treatment of various diseases because of its antioxidant, antiproliferative, immunomodulatory, and anti-infectious activities (Pinheiro *et al.*, 2021). Quercetin has been widely researched by researchers for the prevention and treatment of colorectal cancer.

Quercetin has well-reported prevention effects on various types of cancers including colorectal cancer because of several mechanisms (Singh *et al.*, 2020; Almatroodi *et al.*, 2021; Asgharian *et al.*, 2022; Lotfi *et al.*, 2023). Research states that quercetin has anti-telomerase activities and stops the life span of cancer cells (Bhatiya *et al.*, 2023). They also inhibit the aging proteins and stop the process of increased life of the cancerous cells (Ezzati *et al.*, 2020; Vafadar *et al.*, 2020). Quercetins have been reported to induce apoptosis in cancerous cells including colorectal cancer (Özsoy *et al.*, 2020) and in the mice studies because of anti-telomerase and antiaging activities (Tezerji *et al.*, 2022b). Moreover, they stop the growth of colorectal tumors by arresting the cell division of cancerous cells (Al-Ghamdi *et al.*, 2021; Bhatiya *et al.*, 2023). They affect the genes associated with the protein regulators of the cell division and control the cell cycle at the G1, G2, or G1/S and G2/S stages (Dhupal and Chowdhury, 2020). The cell division must be stopped at early stages to avoid metastasis or perforation in the intestine in colorectal cancer (Xue *et al.*, 2020). Quercetins also help stop the preneoplastic problems of colorectal cancer (Wang *et al.*, 2020b; Hasibuan *et al.*, 2024). The preneoplastic lesions of colorectal cancer include various colorectal polyps and adenomas (Battistone *et al.*, 2021). Additional preneoplastic lesions of colorectal cancer may include the presence of abnormal cells or dysplasia in the colorectal region of the intestine which is especially seen in inflammatory bowel disease (Gui *et al.*, 2020). Moreover, quercetin has been proven effective in reducing the bacteria associated with the etiology of colorectal cancer as well as they are potent antioxidants (Pérez-Valero *et al.*, 2024). Quercetins reduce oxidative stress and potentially reduce the risk of colorectal cancer because oxidative stress is among the major predisposing factors of colorectal cancer (Basak *et al.*, 2020).

All these mechanisms of action have been proven in *in vivo* experiments utilizing several kinds of xenograft rodents (Ahmed *et al.*, 2016; Darband *et al.*, 2018; Tezerji *et al.*, 2022a; Pérez-Valero *et al.*, 2024). Quercetin reduced cell proliferation and inhibited the phenomenon of colorectal cancer by stopping the multiple stages of cancer (Table 2). These studies suggest that quercetin can be used clinically for the prevention and treatment of colorectal cancer.

Resveratrol: Resveratrol is a polyphenol belonging to stilbenoids produced by many plants as a defense substance (Navarro *et al.*, 2018). It is classified as phytoalexin which is termed the phytochemicals used for the protection of plants from external attacks (Tiku, 2020). It is secreted usually in response to injuries, external pathogenic organisms, stresses, and excessive exposure to sunlight (Zhang *et al.*, 2021a). It has proven antiviral, antibacterial antiproliferative, and anticancer properties (Abedini *et al.*, 2021; Kaur *et al.*, 2022).

Resveratrol is among the most widely researched compounds against cancer including colorectal cancer (Rytsyk *et al.*, 2020; Vernousfaderani *et al.*, 2021; Prakash *et al.*, 2024). Resveratrol has been proven to be a preventive, therapeutic, and synergistic compound of chemotherapy for the treatment of all types of cancers including colorectal cancers (Wang *et al.*, 2020c; Unnikrishnan Meenakshi *et al.*, 2024). Resveratrol is known for its cancer protective efficiencies as researchers have reported that it can detoxify the carcinogens responsible for preneoplastic colorectal lesions (Ferraz da Costa *et al.*, 2020; Quiñonero *et al.*, 2023). It has potent antioxidant properties thus preventing oxidative stress-mediated DNA modulations which lead to the development of colorectal carcinomas (Basak *et al.*, 2020; Wu *et al.*, 2023). Additionally, resveratrol has been reported to work as a potent antagonist of multiple enzymes e.g. cytochrome 450 complexes (responsible for cancerous chemical release) (Saiko *et al.*, 2008; Britton *et al.*, 2015), CYP1A1 and CYP1B1 (responsible for activation of procarcinogens), etc (Beedanagari *et al.*, 2009). These enzymes lead to metabolic pathways promoting carcinogenesis in the colorectal region and are inhibited by resveratrol's detoxification mechanisms. Research proves that resveratrol has the potential to control cancer by blocking the cancer-causing chemicals from approaching the target tissues (Cal *et al.*, 2003), hence preventing colorectal cancer. Resveratrol, besides its preventive mechanisms, has the potential to stop colorectal cancer tumors through several mechanisms (Varoni *et al.*, 2016). It has been proven to kill cancerous cells by induction of apoptosis and killing of cancerous cells by the mechanisms involving the Fas and Fas-ligand

regulation (Delmas *et al.*, 2011; Ashrafizadeh *et al.*, 2021; Fu *et al.*, 2021). Moreover, resveratrol has also the potential to prevent the several stages of cancer by blocking the abnormal expression of growth factors and tyrosine kinases (Aggarwal *et al.*, 2004; Varoni *et al.*, 2016). Resveratrol can cease the cell cycle by acting upon various processes and stages in abnormal cell division, which are observed in all types of cancers including colorectal cancer (Rauf *et al.*, 2018; Singh *et al.*, 2019). Resveratrol has been found effective in the prevention and control of several types of cancers including colorectal cancer in mice models (Vernousfaderani *et al.*, 2021; Brockmueller *et al.*, 2024). An interesting property of resveratrol is that it has been found a suitable synergist to the several chemotherapeutic substances used for the treatment of cancer (Arabzadeh *et al.*, 2021; Patra *et al.*, 2021). Resveratrol has been used as a protective agent for cardiovascular, gastrointestinal, and excretory systems along with having promising hepatoprotective activity against chemotherapy-induced issues in experimental animals (Angellotti *et al.*, 2023; Kasim *et al.*, 2023). The literature states sufficient mechanisms of action and with evidence of *in vivo* rodent models that the resveratrol has safe and effective potential to control and prevent colorectal cancer (Schneider *et al.*, 2001; Carter *et al.*, 2014; Honari *et al.*, 2019; Rytsyk *et al.*, 2020; Tezerji *et al.*, 2022a).

Kaempferol: Kaempferol is a compound that has been named because of its major source; the aromatic ginger (*Kaempferia glanga*) (Khairullah *et al.*, 2021). It is also abundantly present in tea, green leafy vegetables, and multiple herbs of medicinal importance (Alam *et al.*, 2020). Kaempferol belongs to the flavonol group of polyphenolic compounds (Berger *et al.*, 2013) and is known for its antioxidant, immunomodulatory, antimicrobial, and multiple other medicinal properties (Periferakis *et al.*, 2023). It has been researched for the treatment of multiple types of cancers including colorectal cancer in *in vitro* as well as in *in vivo* rodent models (Song *et al.*, 2015; Kazmi *et al.*, 2021; Qiang *et al.*, 2021; Nejabati and Roshangar, 2022; Qattan *et al.*, 2022).

Kaempferol, like all other polyphenolics, has cancer-prevention properties because of its anti-inflammatory, antioxidant, and immunomodulatory properties (Sharma *et al.*, 2021; Alrumaihi *et al.*, 2024). It prevents the oxidative stress mediators in the gastrointestinal tract which serve as the predisposing factors to the colorectal cancer polyps (Chen *et al.*, 2023; Ospina *et al.*, 2024). Similarly, kaempferol can affect the various stages of the cell cycle and prevent repeated division of cells along with induction of apoptosis in the cancerous cells (Amjad *et al.*, 2022; Felice *et al.*, 2022). Kaempferol specifically targets focal adhesion kinases (Hung *et al.*, 2017). Focal adhesion kinases are a group of protein-based tyrosine kinases being overexpressed in multiple types of cancers including colorectal cancer at advanced stages (Troiani *et al.*, 2013; Moriarity *et al.*, 2016). Kaempferol prevents their overexpression and along with that, it can stop the AKT phosphorylation (Lin *et al.*, 2013; Jo *et al.*, 2015; Yao *et al.*, 2016). The AKT phosphorylation leads to unmanaged cell division leading to proliferation and metastasis, moreover, AKT phosphorylation resists the induction of apoptosis (Khan *et al.*, 2022). Kaempferol has been found to block the development and metastasis by multiple other pathways (Chen *et al.*, 2013) including inhibition of matrix metalloproteinase-2 enzyme (breaks down extracellular skeletal proteins, hence facilitating cancer cells to cross the boundaries) (Cho *et al.*, 2023).

Luteolin: Luteolin is a yellow-colored flavone flavonoid polyphenol produced by multiple plants and abundantly present in fruits, vegetables, and herbs (Tomou *et al.*, 2023). It is classified as phytoalexin which is termed the phytochemicals used for the protection of plants from external attacks (Tiku, 2020). It differs from quercetin slightly by the addition of an extra hydroxyl group in its chemical structure (Ahmadi *et al.*, 2020). Like other polyphenolics, luteolin is also an anti-inflammatory, antioxidant, and a potent antitumor substance (Singh Tuli *et al.*, 2022; Çetinkaya and Baran, 2023).

Luteolin has a strong antioxidant capacity so it can prevent oxidative stress-mediated DNA modulations which lead to the development of colorectal carcinomas (Basak *et al.*, 2020). Luteolin has prevention effects on various types of cancers including colorectal cancer because of several mechanisms (Ganai *et al.*, 2021; Erdoğan *et al.*, 2022). It has cancer suppression mechanisms as it acts as an anti-telomerase agent and stops the life span of cancer cells (Yadav *et al.*, 2024). They also inhibit the aging proteins and stop the process of increased life of the cancerous cells. Luteolin, like other polyphenolics, induces apoptosis in cancerous cells including colorectal cancer (Song *et al.*, 2022; Yoo *et al.*, 2022). Moreover, luteolin stops the growth of colorectal tumors by arresting the cell division of cancerous cells (Liu *et al.*, 2020). It has been proven to kill cancerous cells by induction of apoptosis and killing of cancerous cells by the mechanisms involving kinase suppression and reducing the cellular transcription activities (Ganai *et al.*, 2021; Hussain *et al.*, 2021). Luteolin has proven antitumor activity in colorectal cancer in mice.

Other polyphenols: Besides these selected compounds several other polyphenolic compounds including tannins, stilbenes, and lignans have been researched against colorectal cancer (Hazafa *et al.*, 2022; De *et al.*, 2023). Generally, all these phenolics are antioxidant and anti-inflammatory substances (Hong *et al.*, 2020). They suppress the oxidative stress in the rectal region hence stopping the development of neoplastic lesions (De *et al.*, 2023). Polyphenols have been reported to have antitumor activities because of their antitelomerase, antiaging, and apoptosis-induction mechanisms (Dariya *et al.*, 2020). Multiple *in vitro* studies prove the potential of these substances for the prevention and treatment of colorectal cancer (Afrin *et al.*, 2020; Ağagündüz *et al.*, 2022). All of these polyphenolics are being searched for their potential to be used as therapeutic and synergists to routinely used anti-cancer therapies, however *in vivo* studies are scarce. All the groups of polyphenolics have the potential to be used in the treatment of colorectal cancer.

Perspectives and limitations: Polyphenols are being widely researched and have been proven to be ideal candidates for the prevention, treatment and adjuvants for

the treatment of colorectal cancer (Osorio *et al.*, 2020; Roszkowski, 2023). Some clinical trials also have been completed proving that the polyphenolic compounds can be used therapeutically (Marino *et al.*, 2020; Bakrim *et al.*, 2022) and the post-clinical formulations containing resveratrol and other compounds are being used as adjuvants for the treatment of colorectal cancer (Bracci *et al.*, 2021; Errante and Neto, 2021). Several nutritionists recommend using of quercetins, resveratrol, kaempferol, and some other polyphenolics in the diet for the prevention of colorectal cancer or elimination initial stage of rectal polyps, however, their use as medicine needs research (AlAli *et al.*, 2021). The main issues that need to be resolved include their delivery, efficacy, and toxicities related to their long-term use (Wang *et al.*, 2020d; Hendawy, 2021). Nano formulations of these compounds are being searched, however, a disease like cancer needs a lot of studies before any recommendation for the clinical use of these drugs (Das *et al.*, 2023).

Conclusions: The review concludes that the current control measures are insufficient for the treatment of the deadly disease of colorectal cancer. It can be caused by multiple factors and its cases and mortalities are increasing every year. Polyphenolics are among the most suitable candidates because of their multiple mechanisms against colorectal cancer in the light of research and clinical use, however, further studies can assist us in finding suitable formulations for the treatment of colorectal cancer.

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