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REVIEW ARTICLE

PHARMACOGNOSY

GINGEROL MIGHT BE A SWORD TO DEFEAT COLON CANCER

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ABSTRACT

The important medicinal part of the ginger plant is rhizome. There are several chemical constitutes present in rhizome, in which [6]-Gingerol, [10]-Gingerol, Zerumbone and Shogaols inhibit Colon Cancer, among these [6]-Gingerol and [10]-Gingerol are very important. In the fresh ginger rhizome, the gingerols were identified as the major active components. Gingerol can remain in two form and this depends upon its structure (the position of the methoxy group) known as [6]-gingerol and [10]-Gingerol. The present review sought to conclude that the phytochemical (Gingerol) have the greater potency on treatment of the various lethal diseases such as colorectal cancer. There are various reports which give the details of mechanism about the inhibitory process of gingerol on colon cancer. Therefore, gingerol might be a new therapeutic agent for the better treatment of human colon cancer for that further research on gingerol is necessary.

KEYWORDS

Zingiber officinale, [6]-Gingerol, [10]-Gingerol, Colon Cancer, colorectal cancer, Leukotrine A4 hydrolase

INTRODUCTION

Nature has been a source of medicinal agents for thousands of years and an impressive number of modern drugs have been isolated from natural sources, many based on their use in traditional medicine. Medicinal plants are of great importance to the health of individuals and communities. Herbal medicines serve the health needs of about 80% of the world's population [1].

Herbal Medicine can be broadly classified into various basic systems: Traditional Chinese Herbalism and Ayurvedic Herbalism. Western Herbalism is today primarily a system of folk medicine [2, 3]. Ginger (*Zingiber officinale* Roscoe, Zingiberacae) is widely used around the world in foods as a spice [4, 5, 6]. The name of the genus, *Zingiber*, derives from a Sanskrit word denoting "horn-shaped". In Sanskrit, ginger is known as Sringavera which has given way to Zingiberi in Greek and to the Latin Zingiber [7, 8]. Ginger has been used as medicine from Vedic period and is called "maha aushadhi", means the great medicine. The important medicinal part of the ginger plant is rhizome. There are several chemical constitutes, in which [6]-Gingerol, [10]-Gingerol, Zerumbone and Shogaols inhibit Colon Cancer. But various evidence are reported on [6]-Gingerol and [10]-Gingerol. Several experiment suggest that [6]-gingerol is effective in the suppression of the transformation, hyperproliferation of cells, and inflammation that initiate and promote carcinogenesis, angiogenesis and metastasis [9,10,11,12,13].

The leukotrienes are derived from the oxidative metabolism of arachidonic acid and are implicated in human cancer and chronic inflammation [14,15]. Suppress of LTA4H provided new direct evidence showing that LTA4H is implicated in the anchorage-independent growth of HCT116 colon cancer cells. Moreover, here [6]-gingerol suppresses tumor growth of HCT116 cells implanted in nude mice by inhibiting the enzymatic activity of LTA4H [16]. Evidence indicates that [6]-gingerol exerts an inhibitory effect on DNA synthesis, also causes apoptosis in human promyelocytic leukaemia (HL-60) cells [17]. In vitro, [6]-gingerol inhibited both the VEGF- and bFGF-induced proliferation of human endothelial cells and caused cell-cycle arrest in the G1phase [18].

In the case of [10]-gingerol, its effect on human promyelocytic leukemia (HL-60) cells is better than [6]-gingerol's [17] and the activity of sarcoplasmic reticulum of Ca^{2+} -ATPase could be stimulated by [10]-gingerol [19]. [10]-Gingerol can induced the formation of the [Ca+2]i which is cytotoxic to the colorectal cancer cell. The main aim to write this review is to give insight on gingerol that might be a target for the researcher for the development of less toxic and most potent therapeutic agent for the better treatment of human colon cancer. In addition, this review might be used for the educational material to the teacher and student who would like to know details about the pharmacognostic and pharmacological properties of gingerol.

Ginger

The useful part of the ginger plant is rhizome. The plant produces an orchid like flower with petals that are greenish yellow streaked with purple colour. Ginger is cultivated in areas of abundant rainfall. Ginger is cultivated in tropical areas also such as Jamaica, China, Nigeria and Haiti. It is mainly

cultivated in Kerala, Karnataka, and Tamil Nadu and North Eastern states [20].

The ginger plant has a perennial, tuberous root or rhizome, where the stems are erect, oblique, round, annual, and invested by the smooth sheaths of the leaves, 2 or 3 feet in height.

Ginger rhizome is typically consumed as a fresh paste, dried powder, slices preserved in syrup, candy (crystallized ginger) or for favoring tea. In many countries, especially in India and China, fresh ginger is used to prepare vegetable and meat dishes and as a flavouring agent in beverages and many other food preparations [21].

Active constituents of ginger

The sensory perception of ginger in the mouth and the nose arises from two distinct groups of chemicals; Volatile oils and Non-volatile oils. The volatile oil components in ginger consist mainly of sesquiterpene hydrocarbons, predominantly zingeberene (35%), curcumene (18%) and farnesene (10%), with lesser amounts of bisabolene, monoterpenoid hydrocarbons, 1, 8-cineole, linalool, borneol, neral, and geraniol and b-sesquiphellandrene. Many of these volatile oil constituents contribute to the distinct aroma and taste of ginger. Non-volatile pungent compounds contain biologically active constituents including the non-volatile pungent principles, such as the gingerols, shogaols, paradols and zingerone that produce a ‘‘hot’’ sensation in the mouth. The gingerols, a series of chemical homolog differentiated by the length of their unbranched alkyl chains, were identified as the major active components in the fresh rhizome [22].

Other constituents are oleoresins, fats, waxes, carbohydrates, vitamins and minerals. Ginger rhizomes also contain a potent proteolytic enzyme called zingibain [23].

Gingerol

Gingerol can be remain in two form depends upon its structure (the position of the methoxy group) known as [6]-gingerol and [10]-Gingerol. Both are the active constituent of fresh ginger which is chemically related with capsaicin and piperine, gives spiciness. It is normally found as pungent yellow oil, but also can form a low-melting crystalline solid [24]. In the fresh ginger rhizome, the gingerols were identified as the major active components and [6] gingerol [5-hydroxy-1-(4-hydroxy-3-methoxy phenyl) decan-3-one is the most abundant constituent in the gingerol series. In dried ginger powder, shogaol a dehydrated product of gingerol, is a predominant pungent constituent upto biosynthesis [25,26&27].

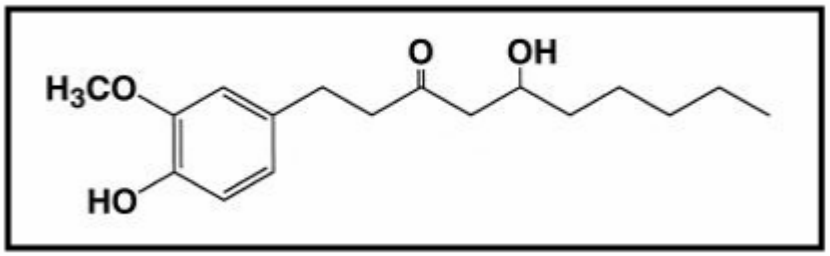

Fig. 1
Structure of Gingerol-[6] [28]

Chul H J *et al* have studied that [6]-gingerol, the major pharmacologically active component of ginger which have antioxidant and anti-inflammatory properties and exert substantial anticarcinogenic and antimutagenic activities [29,30].

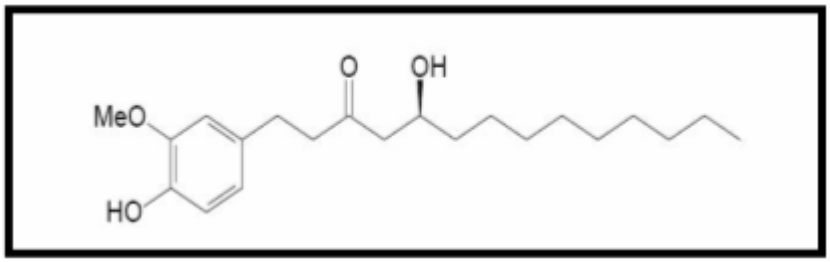

Fig. 2
Structure of Gingerol-[10] [31]

Gingerol-[10] is structurally analog of gingerol-[6]. Its IUPAC Name: (5S)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl) tetradecan-3-one. It also inhibit colorectal cancer by producing cytotoxic reactive compound [Ca2+]i .

Bode A studied that gingerol inhibited the growth of human colorectal cancer cells. The author claimed that these results strongly suggest that ginger compounds may be effective chemopreventive and chemotherapeutic agents for colorectal carcinomas [32]. In a recent study its modifying potential on the process of colon carcinogenesis induced by 1, 2-dimethylhydrazine (DMH) was investigated in male wistar rats using the aberrant crypt foci assay by Dias et al. Results showed that dietary intake of ginger does not significantly changes the proliferative or apoptosis indexes of the colonic crypt cells [33]. The effect of ginger on the initiation and post-initiation stages of DMH-induced colon carcinogenesis in male wistar rats was studied by Manju V *et al.* The results showed a lower incidence of tumors [19].

Colon cancer

The colon is the last part of the digestive system which extracts water and salt from solid wastes. Tumors of the colon and rectum are growths arising from the inner wall of the large intestine. Benign tumors of the large intestine are called polyps. Malignant tumors of the large intestine are called cancers [34].

Cancer occurs when cells become abnormal and divide without control or order. The colon and rectum are made up of many types of cells. Normally, cells divide to produce more cells only when the body needs them. If cells keep dividing when new cells are not needed, a mass of tissue forms which is called a growth or tumor can be benign or malignant. Benign tumors are not cancer. They can usually be removed and, in most cases, they do not come back. Benign tumors are rarely a threat to life. Malignant tumors are cancer. Cancer cells can invade and damage tissues and organs near the tumor. The spread of cancer is called metastasis.

Colorectal cancer is a disease which also known as colon cancer or large bowel cancer. It includes cancerous growths in the colon, rectum and appendix. It is the fourth most common form of cancer in the United States and the third leading cause of cancer-related death in the Western world. Colorectal cancers arise from adenomatous polyps in the colon. These mushroom-shaped growths are usually benign, but some develop into cancer [35,36].

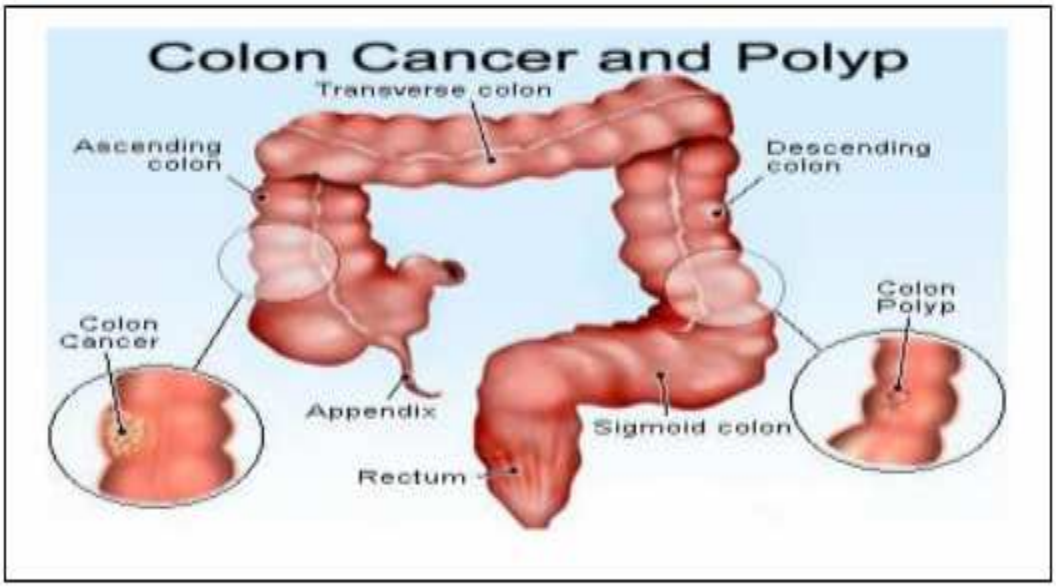

Fig.3
Features of Colon Cancer [37]

Cancers that are confined within the wall of the colon (TNM stages I and II) are curable with surgery. If untreated, they spread to regional lymph nodes (stage III), where up to 73% are curable by surgery and chemotherapy. Cancer that metastasizes to distant sites (stage IV) is usually not curable, although chemotherapy can extend survival. Radiation is used with rectal cancer [38,39].

Pathology of colon cancer

Colorectal cancers arise from adenomatous polyps-clusters of abnormal cells in the glands covering the inner wall of the colon. These abnormal growths enlarge and ultimately degenerate to become adenocarcinomas.

Adenocarcinoma is a malignant epithelial tumor, originating from glandular epithelium of the colorectal mucosa. It invades the wall, infiltrating the muscularis mucosae, the sub-mucosa and thence the muscularis propria. Tumor cells describe irregular tubular structures, harboring pluristratification, multiple lumens and reduced stroma.

Most colorectal cancer tumors are thought to be cyclooxygenase-2 (COX-2) positive. This enzyme is generally not found in healthy colon tissue, but is thought to fuel abnormal cell growth [40].

Staging

Colon cancer staging is an estimate of the amount of penetration of a particular cancer. It is performed for diagnostic and research purposes, and to determine the best method of treatment. The systems for staging colorectal cancers depend on the extent of local invasion, the degree of lymph node involvement and whether there is distant metastasis.

The most common staging system is the TNM (for tumors/nodes/metastases) system, from the American Joint Committee on Cancer (AJCC). The TNM system assigns a number based on three categories. "T" denotes the degree of invasion of the intestinal wall, "N" the degree of lymphatic node involvement, and "M" the degree of metastasis. The broader stage of a cancer is usually quoted as a number I, II, III, IV derived from the TNM value grouped by

prognosis; a higher number indicates a more advanced cancer and likely a worse outcome [41].

Table 1
Details of TNM system are in the table below [41]

AJCC stage	TNM stage	TNM stage criteria for colorectal cancer
Stage 0	Tis N0 M0	Tis: Tumor confined to mucosa; cancer-in-situ
Stage I	T1 N0 M0 T1:	Tumor invades submucosa
Stage I	T2 N0 M0 T2:	Tumor invades muscularis propria
Stage II-A	T3 N0 M0 T2:	T3: Tumor invades subserosa or beyond (without other organs involved)
Stage II-B	T4 N0 M0 T2:	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

Pharmacological consequences of gingerol on colon cancer

Chemoprevention by plant-derived compounds or dietary phytochemicals has emerged as an accessible and promising approach to cancer control and management.

Inhibition of epidermal growth factor-induced cell transformation and activator protein-1 activation

Ginger and its components have been used traditionally for the treatment of gastrointestinal ailments such as motion sickness, dyspepsia and hyperemesis gravidarum, and are also reported to have colon cancer chemopreventive activity. These results strongly suggest that ginger compounds may be effective chemopreventive and chemotherapeutic agents for colorectal carcinomas. In first experiment, mice were fed with ginger before and after tumor cells were injected. In the second set of experiments, ginger was fed only after their tumors had grown to a certain size. The efficacy of ginger was found to be significantly in both cases [9].

Effect of [10]-gingerol on [ca^{2+}] and cell death in human colorectal cancer cells

[6]-Gingerol also induced [Ca^{2+}]i elevation and which was cytotoxic to canine renal cells [42]. But [10]-gingerol inhibits the human promyelocytic leukemia (HL-60) cells better than [6]-gingerol's [43] and the activity of sarcoplasmic reticulum of Ca^{2+}-ATPase could be stimulated by [10]-gingerol [44]. The endoplasmic reticulum is a major Ca^{2+} store in the majority of cells [45]. Various proteins and lipids are synthesized and modified in the endoplasmic reticulum [46,47]. Perturbation of endoplasmic reticulum Ca^{2+} homeostasis,

protein misfolding, or oxidative stress can lead to cell death [47,48]. The acute incubation of [10]-gingerol caused a substantial and lasting (Ca^{2+})i response, this unregulated (Ca^{2+})i rises can be linked to cytotoxicity [45,49], [Ca^{2+}]i elevations can alter many cellular functions [50]. A rise in [Ca^{2+}]i induced by oxidants may activate Ca^{2+}-dependent enzymes such as proteases, nucleases, and phospholipases to facilitate mitochondrial oxidative stress leading to cytotoxicity [51,52]. [10]-gingerol causes a significant concentration-dependent, sustained [Ca^{2+}]i rise in human colorectal SW480 cancer cells. [10]-Gingerol may affect cell physiology significantly by changing Ca^{2+} signaling and stimulating Ca^{2+}-coupled bioactive molecules. [Ca^{2+}]i rise was contributed to by both intracellular Ca^{2+} release and extracellular Ca^{2+} influx, because the signal was suppressed by removal of extracellular Ca^{2+}.

Thapsigargin-sensitive endoplasmic reticulum appears to play a crucial role because the [10]-gingerol-induced Ca^{2+} release was partly abolished by depletion of the endoplasmic reticulumic Ca^{2+} store with thapsigargin, and conversely, pretreatment with [10]-gingerol also inhibited thapsigargin-induced Ca^{2+} release. [10]-gingerol releases Ca^{2+} stored in the endoplasmic reticulum is independent on protein kinase C activity because suppression of this protein did not affect [10]-gingerol-induced Ca^{2+} release. Because [10]-gingerol and thapsigargin share the same Ca^{2+} stores, [10]-gingerol may very likely release Ca^{2+} in a manner similarly to thapsigargin by inhibiting endoplasmic reticulum Ca^{2+} pump. [10-]-gingerol is cytotoxic in several cell types including human A549, SK-OV-3, SK-MEL-2, and HCT15 tumor cells [31].

Inhibition of rat colonic adenocarcinoma cells proliferation and angiogenesis in vitro

Ginger's (Zingiber officinale Roscoe) natural bioactive, specifically ginger extract and [6]-gingerol, were measured for their in vitro inhibition of two key aspects of colon cancer biology--cancer cell proliferation and angiogenic potential of endothelial cell tubule formation. Ginger extract was obtained via column distillation, while the [6]-gingerol was purchased from Calbiochem. Antiproliferation activity was assessed through tritiated thymidine ([(3) H] Tdr) incorporation studies of YYT colon cancer cells; the anti-angiogenic ability of gingerol was assessed by a Matrigel assays using MS1 endothelial cells. These selected ginger bioactives had: 1) a direct effect on YYT rat cancer cell proliferation (6-1.5% ginger extract; 100-4 microM [6]-gingerol); 2) an indirect effect on MS1 endothelial cell function either at the level of endothelial cell proliferation or through inhibition of MS1 endothelial cell tube formation (100-0.8 microM). Compound [6]-gingerol was most effective at lower doses in inhibiting endothelial cell tube formation. These in vitro studies show that [6]-gingerol has two types of antitumor effects: 1) direct colon cancer cell growth suppression, and 2) inhibition of the blood supply of the tumor via angiogenesis. Further research is warranted to test [6]-gingerol in animal studies as a potential anticancer plant bioactive in the complementary treatment of cancer [53].

Anti angiogenesis in vitro and in vivo

Kim E C *et al* has performed that [6]-Gingerol has anti-tumor-promoting activities. They reported its novel anti-angiogenic activity in vitro and in vivo. In vitro, [6]-gingerol inhibited both the VEGF- and bFGF-induced proliferation of human endothelial cells and caused cell cycle arrest in the G1 phase. It also blocked capillary-like tube formation by endothelial cells in response to VEGF, and strongly inhibited sprouting of endothelial cells in the rat aorta and formation of new blood vessel in the mouse cornea in response to VEGF. The results demonstrate that [6]-gingerol inhibits angiogenesis and may be useful in the treatment of tumors and other angiogenesis-dependent diseases [54].

Activity in cell growth arrest and apoptosis in human colorectal cancer cells

[6]-gingerol has been known to possess anti-tumorigenic and pro-apoptotic activities. However, the mechanisms by which it prevents cancer are not well understood in human colorectal cancer. Cyclin D1 is a proto-oncogene that is over expressed in many cancers and plays a role in cell proliferation through activation by β-catenin signaling. Nonsteroidal anti-inflammatory drug (NSAID)-activated gene-1 (NAG-1) is a cytokine associated with pro-apoptotic and anti-tumorigenic properties. The report said that whether [6]-gingerol influences cyclin D1 and NAG-1 expression and determined the mechanisms by which [6]-gingerol affects the growth of human colorectal cancer cells in vitro. The results suggest that [6]-gingerol stimulates apoptosis through up regulation of NAG-1 and G_1 cell cycle arrest through down regulation of cyclin D1 [55].

Suppresses colon cancer growth by targeting leukotriene a_4 hydrolase

The leukotrienes structurally related to paracrine hormones derived from the oxidative metabolism of arachidonic acid. .Leukotriene can provoke human cancer and chronic inflammation [56,57]. Leukotrienes are found at high levels in most inflammatory lesions and are involved in the physiologic changes that are characteristic of the inflammatory process [58]. Leukotrienes, such as leukotriene B4 (LTB4), a potent chemoattractant that induces a forceful inflammatory response, are implicated in cancer development [59,60,61&62]. Because LTB4 have a role in carcinogenesis, where leukotriene A4 hydrolase (LTA4H) act as an attractive target for chemoprevention and cancer therapy [63]. LTA4H is a bifunctional zinc enzyme that catalyzes the final rate-limiting step in the biosynthesis of LTB4. Besides catalyzing the production of LTB4, LTA4H also possesses aminopeptidase activity [64]. LTA4H was shown to exhibit high levels of protein expression in certain types of cancers, and its inhibition leads to reduced cancer incidence in animal models [65,66]. LTA4H caused carcinoma in the HCT116 cell in the colonrectal cancer.

[6]-Gingerol directly binds with LTA4H, [6]- gingerol inhibits LTA4H enzyme activity. The secreted LTB4 levels in HCT116 and HT29 cells. [6]-gingerol suppresses LTB4 production in both cell lines. The inhibitory effect of [6]-gingerol against aminopeptidase activity was further evaluated in vitro by using a p-nitroanilide derivative of alanine (Ala-p-NA) as substrate. The aminopeptidase activity of LTA4H was also potently suppressedby [6]-gingerol. [6]-gingerol suppresses tumor growth of HCT116 cells implanted in nude mice by inhibiting the enzymatic activity of LTA4H. These data indicate that LTA4H might be a highly desirable target for the prevention of colorectal cancer.

Chemopreventive efficacy of ginger (*zingiber officinale*) in ethionine induced rat hepatocarcinogenesis

The effect of ginger on the initiation and post-initiation stages of DMH-induced colon carcinogenesis in male Wistar rats was studied, where the results showed a lower incidence of tumors. It was further concluded by the researchers of same group that ginger supplementation suppressed colon carcinogenesis by reducing lipid peroxidation and significantly enhancing the enzymatic and non-enzymatic antioxidant levels [20].

Lack of chemopreventive effects of ginger on colon carcinogenesis

In a recent study its modifying potential on the process of colon carcinogenesis induced by 1, 2-dimethylhydrazine (DMH) was investigated in male Wistar rats using the aberrant crypt foci assay. Results showed that dietary intake of ginger does not significantly changes the proliferative or apoptosis indexes of the colonic crypt cells [33].

CONCLUSION

The present review sought to conclude that the phytochemical (Gingerol) have the greater potency on treatment of the various lethal diseases such as colorectal cancer. There are various reports which give the details of mechanism about the inhibitory process of gingerol on colon cancer. There is also negative feedback of gingerol in certain cases where colon carcinogenesis induced by 1, 2-dimethylhydrazine (DMH). But we found several reports which give the positive result to overcome the effect of colon cancer. Since, there is no good medicine till now for the treatment of colon cancer, and also there are lots of side effects of radiotherapy and chemotherapy so more studies are also required on the kinetics of gingerol and its effects of their consumption over a long period of time. So further evaluation of this phytochemical (Gingerol) as a novel drug, we have to carry out more scientific researches and development of the chemical entities as a drug for the colorectal cancer. Therefore, gingerol might be a new therapeutic agent i.e. anti-angiogenic agent for the better treatment of human colon cancer, for that further research on gingerol is essential.

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