Research

International Journal of Clinical and Medical Case Reports

Preventive and Therapeutic Effect of Ellagic Acid, Sulforphane and Ursolic Acid on Colon Cacner: From Cellular Response to Molecular Mechanism of Action With Future Perspectives

Jaman S[1], Md. Islam N[2], Maniruzzaman[3], Hossain F[4], Bhuiyan RH[1] And Nasim M[5]

[1]Department of Biochemistry and Molecular Biology, University of Rajshahi-6205 [2]Department of Biochemistry and Molecular Biology, Bangladesh University of Health Sciences. [3]Department of Pharmacy, Varendra University, Rajshahi-620 [4]Department of Biotechnology and Genetic Engineering, University of Development Alternative

Department of Pharmaceutical Sciences, North South University, Bashundhara, Dhaka, Bangladesh.

[5]Department of Pharmaceutical Sciences, North South University, Bashundhara, Dhaka, Bangladesh

[*]**Corresponding Author:**

Sadikuj Jaman, Department of Biochemistry and Molecular Biology, University of Rajshahi-6205,

Tel: +8801722793579,

Email: sadik09bio.ru19@gmail.com

Received Date: 28 Dec 2023

Accepted date: 12 Jan 2023

Published Date: 23 Jan 2023

1. Abstract

Over the world older men are more victim than women for colon cancer and thought third most common type of cancer. Due to the relation with digestive tract with food supply is most important factor with natural diet. Currently, Patients are treated in many numerous ways. Including multidrug resistance, recurrence and lack of treatment for metastases are the main issues in the treatment of colon cancer. Surgery, Chemotherapy, Hormone therapy and radiotherapy are frequently accompanied by adverse effects. Due to their safety, dietary phytochemicals have become effective tools for the treatment and prevention of cancer in recent years. In widely consumed fruits and vegetables Ellagic acid (EA), Sulforaphane (SF), Ursolic acid (UA) have been reported to suppress colon cancer cell proliferation and cause apoptosis. The role of EA, SF and UA in the battle against colon cancer is covered in this review. These agents have been shown to have effects both in vitro and in vivo.

2. Keywords:

Colon cancer, Ellagic acid, Sulforaphane, Ursolic acid, in vitro, in vivo. Caco-2, SW620

3. Abbreviations:

AKT, protein kinase B; Apaf-1, apoptotic protease activating factor 1; AIF, apoptosis inducing factor; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2 associated X; Bad, Bcl-2 associated agonist of cell death; CDK4, cyclin-dependent kinase 4; CDC2, cell division cycle2; COX-2, cyclooxygenase-2; CYP19/1A1/1A2, cytochrome P45019/1A1/1A2; DNMT1/3a, DNA (cytosine-5)-methyltransferase 1/3a; DMBA, 9,10-dimethyl-1,2-benzanthracene;epidermal growth factor; EGFR, epidermal growth factor receptor; FoxM1, forkhead box M1; GSTA1, glutathione S-transferase A1; HDAC, histone deacetylases; HER2, human epidermal growth factor receptor 2; hTERT, human telomerase reverse transcriptase; JNK, jun N-terminal kinase; LC3, microtubule-associated protein light chain 3; mTOR,mammalian target of rapamycin; MMP-2, matrix metalloproteinase-2; MAPK, mitogen-activated protein kinases; NQO1, NAD(P)H quinone dehydrogenase 1; PTEN, phosphatase and tensin homolog; RARbeta2, retinoic acid receptor beta2; STAT3, signal transducer and activator of transcription 3; TrxR1, thioredoxin reductase 1; VEGFR-2, vascular endothelial growth factor-2. CRC: Colon cancer cell.

4. Introduction

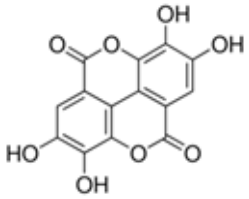
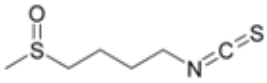
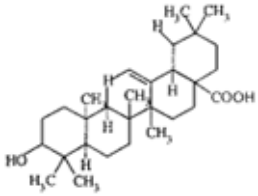
Colon canceris a global health concern. It is the most thirdcommon cancer and the leading cause of cancer-relateddeath among across the world, accounting for 1.09 million of all cancer cases and 551,00 of all cancer deaths [1]. There are currently several treatment options for colon cancer, including surgery, chemotherapy, hormone therapy and radiotherapy. Unfortunately, these current treatments do not always effectively combat the disease and they have had only a minor effect on the cancer's notable morbidity. In addition treatments like radiotherapy, hormone therapy and chemotherapy frequently have negative effects and tumor recurrence can occasionally occur after the tumor has been surgically removed. Another issue with treating colon cancer is multidrug resistance [2].

As a result, colon cancer therapy still presents a challenge and reducing the prevalence of colon cancer requires the creation of efficient medications. Dietary phytochemicals have recently gained popularity as beneficial cancer prevention and treatment agents because they are less toxic, less expensive and have fewer adverse effects than manufactured medications. Colon cancer is strongly tied to diet thus researcher have discovered numerous natural medicines in food supplies. Studies have also revealed that these phytochemicals are crucial in the prevention of colon cancer as well as other types of cancer. Numerous phytochemicals have demonstrated potential anti-colon cancer via modifying cell division, apoptosis, oxidative stress, inflammation, angiogenesis and a number of cell signaling pathways [3]. The effectiveness of several dietary

International Journal of Clinical and Medical Case Reports

phytochemicals in colon cancer prevention and treatment was examined. [4]The dietary phytochemicals Ellagic acid (EA), Sulforaphane (SF), and Ursolic acid (UA) have undergone extensive research and have drawn attention because of their wide range of biological actions and molecular targets. EA was discovered in many fruits as a phytochemical, and the proof was gathered (Table 1). EA has received the most attention among the phenolic acids in oncology, particularly colon cancer. Many cruciferous vegetables, which are widely believed to be popular worldwide, also contained SA as isothiocyanate and this proof was demonstrated in (Table 1).

Table 1: Natural and cheap food sources and their organic structure of EA, SF, and UA

Organic name	Chemical structure	Origin	Common food supplies
Ellagic acid		 pomegranate	Strawberries,raspberries, cranberries, blackberries, pecans, pomegranate, muscadine grapes and walnuts
Sulforaphane		 mustard	Broccoli, brussels sprouts, cabbage, cauliflower, collard, kale, mustard, rutabaga and turnips
Ursolic acid		 peppermint	Apples, bilberries, cranberries, holy basil, peppermint, rosemary, oregano and prunes

5. Introduction With Biological Sources And Their Mode Of Action Of Ellagic Acid, Sulforaphane, And Ursolic Acid

Chemically, EA is hydrophobic. As a result, its sources only have trace levels of it. The gut microbiota converts EA into different urolithins. Which circulate in the blood as glucuronide and sulfate conjugates in the plasma and bile. EA is easily absorbed by the circulatory system. [6] Numerous biologists have also proven the presence of urolithins and their conjugates in the human prostate. While Urolothin A is present in the tissues of the prostate gland, colon and intestines, Urolithin A glucuronide is only present in the tissues of the mouse liver and kidney. Urolithin A is also present in the tissues of the colon, intestine.[7]The mercapturic acid pathway is connected to the conjugates made by the metabolism of SF. Conjugates are formed by SF before it interacts with glutathione. The final result of the enzymatic reaction between cyctein and cysteinylglycine is N-acetyl cysteine conjugates. [8] The analysis of human urine revealed that it included 75 SF, 1% SF-glutathione conjugate, 1% SF cysteinylglycine conjugate, 28% SF-cysteine conjugate, and 65% SF-N-acetlycysteine conjugate. [9,10]After SF was given orally in the mouth, the greatest concentrations were discovered to be in the stomach and bladder, respectively. However, very little amounts of SF were discovered in the gastrointestinal system, prostate, rectum, colon, heart, kidney and other organs. [11] Following oral administration of 5 or 20 mole to mice, the areas with the highest concentrations of SF were discovered to be the small intestine, prostate, kidney and lung. [12] Additionally, following oral administration of 150 mol SF, which was also detected in rat mammary gland tissue (18.8 pmol.mg tissue), and plasma (60M). [13] It is clear that there is minimal UA in biological sources since UA metabolizes quickly and has a low capacity for solubility. [14] The UA content in rat plasma was exceedingly low despite the high oral UA dose (80.32 mg/kg). This suggested that UA has high organ bonding activity and poor blood dispersion. Another possibility was that UA has low bioavailability because it is broken down by the liver and gut wall and is inefficiently absorbed by the intestine. [15] After injection, UA has been detected in human plasma. [16]

6. Ellagic Acid, Sulforaphane, Ursolic Acid, And Colon Cancer

6.1. Ellagic acid

6.1.1. Natural Origin. Pomegranate, muscadine grapes, walnuts, and strawberries was found EA (2, 3,7,8-tetrahydroxy-chromeno [5,4,3-cde]

chromene-5,10-dione). [17]

6.1.2. Biological effects

In vitro studies

CACO 2 Cell line is examined and several resultswere found by treating EA. During Oxidative Stress Colon cancer cell involves with chronic intestinal inflammation and related with redox transcription factors and barrier permeabilization. Dietary food plays a good role in intestinal inflammation modification. Amon of them EA (Ellagic acid) is thought plant bioactivates which helps inhibition of bowel disease in animal models. EA inhibits tumor necrosis factor alpha (TNF-α) induced inflammation in the presence of 10 ng/ml or different EA concentrations. As well as (TNF-α) acts as precursor of (IL) 6 and 8 or release into medium. As a result, 9IC 50= 17.3 Mm FOR IL6 led to increase ICAM-1 and NLRP3 expression, NF-Kb AND erk1/2 activation and mlck gene expression and MLC phosphorylation. [18] EA treated with HCT15 Cell line promoted cell cycle arrest substantially at G2/M phase. EA treatment also support to decrease alkaline phosphatase and lactate dehydrogenase treatment by cytotoxic treatment and anti-proliferative way also it helps to increase 2,7 dichlorodihydrofluorescein diacetate (H2DCF-DA). EA strongly decrease phosphatidylinositol 3-kinase (PI3K)/Akt pathway and their expression guide Bax, caspase-3, and cytochrome c, suppression of Bcl 2 activity.[19]EA also applied in HT29, HT116 and COCA2 cellline and wnt/beta-catenin pathway also activated. This helps to decrease cell viability and CDK8, surviving, c-Myc and cyclin D protein expression downregulated in same time some factor is upregulated like beta catenin, axin1 and 2. [20] [21] EA Show potential on HCT 116 cells and DEGs gene is altered for TGF- β1/Smad3 channel. Generally DEGs gene was identified through cDNA microarray analysis and five genes associated with TGF- β1/Smad3 signaling pathway. This signaling pathway was assessed by TGF- β1 small interfering RNA and SIS3 and a Smad3 inhibitor. The expression patterns of downstream DEGs could altered the TGF- β1/Smad3 Signaling pathway and this pathway may underline the molecular mechanism in CRS cells. [22]Ellagic Acid is thought one kind of quercetin which is compound known as flavonoids. When EA is treated with SW480 colon cancer cells then the result was found in decreased expression of three proteins and the increased of one protein. Type II cytoskeletal 8 keratins and NADH dehydrogenase, Fe-S protein 3 were identified and other protein was not identified by scientists. This increased action is thought the annexin family. Those proteins were identified to have altered expression in the treatment of flavonoid could thought the marker of chemo preventive action against EA. [23]Several study demonstrated that COLO 205 and CACO 2 cells express cytotoxicity result against ellagic acid. HM 251 and HM 233 respectively give good synergistic effect against EA the value of 2.5 – 5 mg/mL. [24]

Table 2: Effect of EA on colon cancer cells

Cell line	Model	Dose/duration	Effect	Mechanism	Reference
CACO 2 & HT29	In vitro and In vivo	In vitro and In vivo	Mitigate intestinal inflammation, loss of intestinal barrier function, increased oxidant production.	↓NFKB ↓ERK1/2	[18]
HCT 15	In vitro and In vivo	20 and 35 µg/mL; in h	Induced apoptosis and cell cycle arrest at G2/M phase. Ant proliferative and cytotoxic effect.	↓PKI3/AKT, ↓BCL2	[19]
HT 29,	In vitro	10 to 20 µM;	Reduced cell viability, and	↓CDK8	[20], [21]
HCT 116 and CACO 2			reduced tumor size in mice, modulate wnt/β catenin signaling cascade protein.		
HCT 116	In Vitro	20 – 35 µg/mL	Increased apoptosis and cell cycle arrest at G0/G1 phase	↓DEGs	[22]
MCF-7 and Hs 578T	In vitro	20 µM	Chemo protective action of quercertin	↓FES protein 3, ↓NADH dehydrogenase, ↓TYPE II cytoskeletal 8 Keratin	[23]
COLO 205, CACO 2, HT 29z	In vitro	2.5 – 5 mg/mL 48h	Anti colitic agents	↓HM251 and HM233	[24]

6.2. Additive or synergisticeffect of EA with other phytochemicals and therapeutic agents

EA has been shown to increase the effectiveness of phosphoinositide 3-kinase (PI3K) inhibitor GDC-094. EA plus GDC-0941 treatment prevented cell proliferation, migration, and invasion by reducing neural precursor cell expressed developmentally down-regulated protein 9 (NEDD-9), cyclooxygenase-2 (COX-2), interleukin-13 receptor subunit alpha-2 (IL-13Rα2) expression. [25]However, the synergistic effect with EA and other phytochemical effect still unclear for colon cancer cell line. But many studies targeted antitumor function and inhibits endometrial cancer. Several methods are used like bioinformatics analysis tools including DrugBank, STRING, WebGestalt and cBioPortal and the main target is to identify PIK3CA, PIK3R1. In addition,this treatment also reduced selected pro-inflammatory cytokines/chemokines including interleukin 8 (IL-8), regulated on activation, normal T cell expressed and secreted (RANTES), and platelet-derived growth factor subunit B (PDGFB), leading to reduction of inflammation. [26]

6.3. Effect of EA after encapsulation

It was argued and informed that this natural food supplement reacts in digestive tract or colon cancer cell which induced apoptosis and reduced AKT/mTOR activation. [27]

In vivo studies

Animals model of EA was introduced by scientists for colon cancer cell line.Several Animal models were studied and colon cancer was accounted for 20 most frequent cancer diseases worldwide and always scientist demand to bring new therapeutics with new mechanism of action into the clinical practice. The number of in vitro and in vivo evidences proved that exogenous changes in pathologically imbalanced microRNAs (miRNAs) are capable of transforming the cancer cell phenotype. About more than 400 original articles 26 was found to assess the effect of miRNA mimics, precursors, expression vectors or inhibitors administered locally or systemically being an approach with relatively high translational potential. This finding was summarized in the field of pharmacokinetics and toxicity of miRNA-based therapy. [28] MicroRNA (miRNAs) are small non-coding RNAs 18-25 nucleoids in length that downregulate gene expression apoptosis, differentiation and development. Functional studies indicate that miRNAs act as tumor suppressors and oncogenes. There are many studies was investigating the ability of miRNA expression profiles to predict prognosis and response to selected treatment in CRC patients. [29]

About 19 downregulated and 18 upregulated miRNAs was studied in CRC patients and five most expressed miRNAs (miRNA-10a-5p, -21-5p, -22-3p, -143-3p, -143-3p and -192-5p) inside a pool of 523 miRNAs from 88 CRC samples. The miRNA-143-3p and miRNA-192-5p are part of clusters related with the oncogenes, deoxynucleic acid (DNA0-repair genes, and genes from the WNT and MAPK signaling pathways. miRNA-221 inhibits the angiogenesis activity through its binding to the c-kit, stat-5A, endothelial nitric oxide synthase and ETS1 mRNAs and the miRNA-29a is associated with the cell cycle arrest another miRNA-21 involves with tumor initiation, increasing the invasion and the metastasis and the miRNA-26b is related with colon cancer growth. [30]EA on the expression of miRNAs was observed. EA treatment downregulated theexpression hsa-miR-1, hsa-miR-139-5p, hsa-miR-145, hsa-miR-195, hsa-miR-363, hsa-miR-378, hsa-miR-378c, hsa-miR-383, hsa-miR-422a, hsa-miR-486-5p, hsa-miR-490-3p, hsa-miR-551b, hsa-miR-628-3p, hsa-miR-628-5p, hsa-miR-1297, hsa-miR-3151, hsa-miR-3163, hsa-miR-3622a-5p, hsa-miR-3656and upregulated the expressionhsa-miR-7,hsa-miR-96, hsa-miR-105, hsa-miR-135b, hsa-miR-296-3p, hsa-miR-483-3p, hsa-miR-493, hsa-miR-549, hsa-miR-552, hsa-miR-584, hsa-miR-592, hsa-miR-1247, hsa-miR-1269, hsa-miR-1827, hsa-miR-3144-3p, hsa-miR-3177, hsa-miR-3180-3p, hsa-miR-4326. [32]EA also reduced the expression of their targets ERα (miR-206), cyclin D1 (miR-206), cyclin G1 (miR-182, -122), Bcl-w (miR-122), Bcl-2 (miR-122), and increased the expression of their targets RASD1 (miR-182), FoxO3a (miR-182), FoxO1 (miR-182, -183), and thereby caused the inhibition of tumor growth. [32] Approximately 650miRNAs identified miR-206 a low abundance miRNA the most significantly altered miRNA in carcinogen-induced rat colon tumors. [33] EA presents in fish oil and pectin in little amount which act as nutritional bioactives that modulate microRNA molecular switches in the colon. This investigation modulated by carcinogen and diet treatment. Aprague awley rats were fed diets containing corn oil and fish oil with pectin cellulose or injected with azoxymethane or saline. Colonic mucosa was used to identify early time of cancer progression [34].

6.4. Sulforaphane

Sources. SFisfound in cruciferous vegetablessuch as broccoli, Brussels sprouts, and cabbage The Chemical Structure is (1-siothiocyanato-4-methylsulfinylbutane). [35]

Biological effects

In vitro studies

SF derived from broccoli may exhibit chemo preventive properties by inducing cell cycle arrest via induction of cyclin-dependent kinase inhibitor 1A ((p21(waf1/cip1)) the key role of the transcription factor kruppel-like factor 4 (KLF4) in mediating the induction of p219waf1/cip1) and cellular differentiation. In CACO2 cells small interfering RNA knock down of KLF4 expression attenuated induction of p21 9waf1/cip1) in response to SF treatment. Otherwise SF reduced sucrose isomaltase activity.[36]CACO2 cell line were treated with 5 micromol/L SF and western blot and real time PCR showed that Nrf2, AKR1C1 and NQO1 protein expressions were increased. Interestingly within 8 hrs Nrf2 protein increase and after 16 hrs. AKR1C1 and NQO1 protein increase that result involve with induction of colon cancer and inhibitor of Nrf2-ARF signaling pathway. SF found in Crude IL-GPE and this extract was treated on HT29 cell line. Pathway involve on colon cancer cell line was amino acid metabolism, aerobic glycolysis, urea cycle and ketone body's metabolism that contribute to energy metabolism and cancer cell. [37]

International Journal of Clinical and Medical Case Reports

Anthocyanins are a flavonoid like SF that are used to treated colon cancer cell HT29 and good result found in in vivo and in vitro, the tumor weight decrease in mouse model. That proved that it downregulated the expression of PI3K and AKT expression and phosphorylation, promoted apoptosis and inhibited colon cancer growth which mechanistically enhanced Bcl-2/Bax and caspase dependent apoptotic pathway targeting the PI3K/AKT/surviving pathway [38] Chemomile extract contain different flavonoid including SF which was treated on HT29 cell and mouse model and found the prodection of MPO, 5 HT, IL-6, NF-kB, TNFα, PGE2, 8-iso-PGF2α after inflammatory stimulus. [39] Sulphonomide derivatives found most cytotoxic activity on MDA-MB-231 and HT29. Another SF treated on wnt/beta catenine pathway resulted growth inhibition apoptosis and increased nuclear translocation of beta catenin. Beta-catenin siRNA markedly increased mRNA and protein levels of c-Myc compared with control siRNA. Beta-catenin siRNA significantly inhibited the expression of Bax and Bcl-2 in celastrol-treated HT29 cells.[40] Salvia extract has been shown protective effects on HCT15 and CO115 cell line. This extract induced DNA methylation on both cell and its tea also act as best oxidative and alkylating DNA damage.[41] Medicinal plants contain SF and is used as functional foods and nutraceuticals control colon cancer cell progression by modulating molecular targets of the PI3k/Akt and MAP kinase signaling pathways.[42] SF also found in salfosa fructosa extract and human breast cancer and colon cancer treated with IC50 valo 66.6 uM and downregulation saw NF-κB, PI3A and upregulation was seen MAPK and TNF-α moreover this extract lead apoptosis with low cytotoix effects on non-tumoral 3T3-L1 cells. So this extract is used in pharmaceutical industries. [43]

Table 3: Effect of SF on colon cancer cells

Cell line	Model	Dose/duration	Effect	Mechanism	Reference
CACO2, HT29	In vitro	IC_{50} 25 and 50 µM	Induction of P21(waf1/cp1), Partly KLF4	↓KLF4, ↑p21(waf1/cip1)	[36]
CACO2	In vitro	5 µmol/L, 8 h	developing inhibitors of Nrf2-ARE signaling pathway.	↑ Nrf2, ↑AKR1C1, ↑NQO1	[37]
HT29	In vitro& In vivo	50 and 75 µM	inhibit the cell viability and proliferation and promote the apoptosis		[38]
HT29	In vitro & In vivo	2 mg/mL	antioxidant and anti-inflammatory properties	↑ NF-κB, ↑PGE2, ↑8-iso-PGF2α, ↑ IL-6	[39]
HT29	In vitro	100 µM, 24 h 25 µM,	Induced apoptosis, cell inhibition	↑beta catenine, ↑C-Myc, ↓Bax, ↓Bcl-2	[40]
HCT15 and CO115	In vitro	25 µM,	Methylating and alkylating DNA damage and apoptosis	↑p21	[41]
CACO2 and HT29	In vitro	25 µM,	Methylating and alkylating DNA damage and apoptosis	↓AKt/PkB, ↓RAS, RAF, ERK1/2,	[42]
RKO and	In vitro	25 µM,	Reduced oxidative stress	↓NF-κB, ↓PI3A,	[43]
Caco-2, MCF-7 and MDA-MB-231			and anti-cancer activity. antioxidant, antitumor and pro-apoptotic effects	↑MAPK, ↑TNF-α	

6.5. Additive or synergistic effect of SF with other phytochemicals and therapeutic agents

SF used in combination with MEK inhibitor and 5 FU treatment and this therapy based on KRAS or BRAF mutant colon cancer models. SF enhanced apoptosis and decreased anchorage –independent growth and induction of thymidine kinase 1, altered mRNA expression in groups of genes. SF 25mg/kg weight and 5-FU 10or 30 mg/kg administered. Colo205 and HCT8 models decreased expression of ki67 was observed in tumors from mice. [44]SF treated on invitro two dimensional cohort migration model such as L 10 cell of human rectal adenocarcinoma cell line. This effect found by TGF beta 1 upregulated in co-cultured conditions and this condition associated with increased production of motility EDA+FN by L-10 cells and blocking FN with specific antibody effectively inhibited the synergistic effect.[45]Caco-2 cells were pretreated with SF and measure TER and 4-kDA FITC dextran (FD4) flux and analyze junction protein expression and structure. This treatment decreased occluding and ZO1 miR-200c-3p and protein expression. While suppression of miR-200c-3P increased expression of PTEN protein and decrease expression of phosphorylated PI3K and AKT proteins and miR-200c-3p overexpression or suppression effect on negative mediator PTEN, maintain TJ function and ameliorates LPS induced intestinal epithelial barrier dysfunction. [46] Galangin cotain anti-cancer and antioxidative properties. Berberine contain same anti-cancer properties and both extract result in cell growth inhibition, apoptosis and cell cycle arrest at G2/M phase with increase ROS level and decrease expression of wnt3a and β-catenine. Induce apoptosis in colon cancer cell line invitro and invivo. [47]

Down-regulation of E-cadherin and upregulation of vimentin, α-SMA, snail and ZEB1 and increase migration of HCOEPICs with over expression of Smads involve with Smad2, Smad3, p-Smad3 and Smad4 then abolish by TGF-β and the inhibition of psmad2/smad2 and p-Smad3/Smad3 also dose dependent. SF induced CCD-18CO suppressing activity of TGF-β/Smads signaling pathway. [48] 5FU 10 or 30mg/kg, 7 days and combination with SF 10 or25mg/kg, 7 days on COLOC205 and HCT8 related with salvage pathway and effects in KRAS or BRAF colon cancer cell line. Induced cell death and enhanced apoptosis, induce of thymidine kinase 1, altered mRNA expression. [49] essential oils oleo gum resin extract act as anticancer agents for in vitro and in-vivo act as growth inhibitory effects towards human colon cancer cell line HCT 116 and LIM1215 with IC50 values 17.82 and 18.86 µg/mL. Downregulated expression of proteins surviving, XIAP, HSP27, HSP60 and HSP70 and upregulated expression of ROS, caspase-3/7 and TRAIL-R2, invasion, reduction, migration and colony formation potential was examined. [50]

In vivo studies

Sulforphan inhibit the secretion of pro-inflammatory cytokines including IL6. Production in response to bacterial lipopolysaccharide (LPS) in human cancer HepG2, suppressed LPS-induced transcription and secretion of IL-6 after 2 µM, 24 hrs. Potential usage of broccoli derived SF as a functional food ingredient in the inflammation induced hepcidin and reducing liver cancer risk development and colon cancer cell. [51] SF enhanced antitumor effect of irinotecan and prevented the occurrence of intestinal damage by modulating and reducing pro inflammatory microbiota. TGF- β leakage was reduced and inhibited PI3k/AKT pathway activation, tumor apoptotic autophagy promoted and inhibited tumor growth and invasion. [52] expression of Nrf2 in colon cancer cell and explore the effect of Nrf2 modulation alone or combination with HCT116 and CT26 cell line in vitro and in vivo study. This cell line revealed Nrf2 siRNA and brusatol, to inhibit Nrf2, decreased viability and sensitized cell to toxicity. Subcutaneously and orthotopically allografted mice result in an average 8-fold reduction in luminescent study end point. [53] SF found in cruciferous vegetable that possess antitumoral properties in carcinogen treated rats. Regulate phase II enzyme, cell cycle and induction of apoptosis and cell cycle arrest in HT29 human colon carcinoma cells. Increase G2/M phase observed increased cyclin B1 protein levels. Preincubation of HT29 cells with roscovitine, cdc2 kinase inhibitor, blocked G2/M phase and cdc2 kinase could be a key target of SF regulation of G2/M block and apoptosis, retinoblastoma tumor suppressor protein (Rb) is highly phosphorylated, Inhibition of proteasomal activity through the use of MG132 diminished SF induced HT29 cell death, apoptotic effect requires a functional proteasome-dependent degradation system. [54] Sinapis alba Linn seeds possess antitumor properties, efficacy of novel mucilaginous fraction of mustard seeds in inhibiting colonic preneoplastic changes in vivo study. There two separate study seen male and female obese rats injected 15 or 10 mg/lg weight for 2 weeks and mustard 5% for 8 weeks. Measure the ability to modulate aberrant crypt foci and obesity associate colon cancer. This research provide impetus to conduct research to understand the underlying mechanism of action.[55]Red cabbage is an important source of vitamin, micro and macroelements and polyphenol including sulforphan. Evaluated anti-inflammatory effect in mouse models determined using clinical, macro and microscopic parameters of inflammation and mechanism of action, expression of pro-inflammatory cytokines and oxidative stress. [56]) These extract as a potential dietary supplement in inflammatory boil disease.

6.6. Ursolic acid

Sources:apples, rosemary, and holy basil contain UA (3-beta-3-hydroxy-urs-12-ene-28-oic-acid). [57]

Biological effects.

***In vitro* studies**

Fruits and vegetable is thought good for colon cancer. Caco2 cells response good protection with ursolic acid, a triterpenoid and luteolin. Extract of fruit and vegetable treated 24h and DNA DNA substrate containing specific damage was seen that these compound not only protect from oxidative damage but also increase repair activity. [58] Rosemarinic acid contain many flavonoid and UA, have been used to treat mouth inflammation and gastric problem. These extract increase β-glucoronidase/sulfatase which is good for measurement of permeability across human intestinal epithelial Caco-2 cell monolayers. [59] UA inhibit cell proliferation on HT29, SW480 and SW620 cell and result got with cell cycle arrest by

alteration of cell cycle protein expression and UA induced apoptosis. P53, p21 protein expression increase and Bcl2 decrease by inhibition of proapototic protein. UA induce cytochrome C and caspase activation. [60] Cell growth arrest at the S- and G2/M phases seen by treatment of dietary polyphenol. Transcriptional profiling and functional analysis changes in the expression levels of MAPK signaling genes k-Ras, c-Myc and CCNB1, CCNB1/P1 gene related with cell cycle arrest and apoptosis. [61] UA induced on HT-29 by playing role in COX-2 overexpression. This overexpression is mediated by p38 MAP kinase pathway as inhibiting its activation using a p38 specific inhibitor or COX-2 specific siRNA. UA treated delay death of HT-29 cells by overexpression of COX-2. [62] UA treated on gastric cancer cell line BGC-803 and hepatocellular cancer cell H22 xenograft in vitro in dose dependant and time dependant manner. G0/G1 stage arrest seen both in invitro and invivo. UA upregulate caspase-3, -8, -9 and downregulate Bcl2. The expression of caspase-3 and -8 was elevated in tumor cells from xenograft treated with UA and this treatment associate with colon cancer cell in vitro and in vivo by decreasing proliferation and inducing apoptosis. [63] MAPK/ERK/or PI3K signaling pathways related on colon cancer cell carcinoma by mutation of KRAS and BRAF. UA and dietary phytochemical treated on HCT15 and CO115 cell line and cell proliferation and apoptosis measured. These research seen that dietary phytochemical have anti proliferative and proapoptotic effect on KRAS and PI3k but not on BRAF. [64]UA or OA 60 µmol/L at 24 or 72 h treatment number of cell death and fragments seen but highest death cell calculation was found in 72 h. UA cytotoxicity more than OA at 30 µmol/L ar 78h. G0/G1 cell cycle arrest was seen on HCT15 cells with UA 30 and OA 60 for 36, 72h with decrease of cell population in S phase and no detectable apoptotic fraction. [65]

Table 4: In vitro Effect of UA on colon cancer cells

Cell line	Dose/duration	Effect	Mechanism	Reference
CACO2	100 µM; 24h	Protect DNA from oxidative damage		[58]
CACO2	50 µM; 24 h	Intestinal glucoronidation/sulfatation	↑β-glucuronidase/sulfatase	[59]
HT29, SW480, SW620	60 µM; 48 h	Anti-cancer potential and apoptosis.	↓p53, ↓p21, ↑Bcl2	[60]
CaCo2	80 µM; 48 h	Potential chemopreventive target.	↓K-Ras, ↓C-Myc, ↑DUSp6, ↑Fos,	[61]
HT 29	30 µM; 72 h	Induced apoptosis	↑p38, ↓Cox 2	[62]
COLO115, HCT15	80 µM	Inhibit cell growth in vivo and vitro by reducing cell proliferation and induction of apoptosis.	↑caspase 3, ↑caspase 8, 9 ↓Bcl2	[63]
HCT15, Co115	150 µM, 72 h	Ant proliferative and proapoptotic effect on mutated colon cell	↓PI3K, ↑Akt	[64]
HCT 15	30 and 60 µmol/L, 48 and 60 h	Inhibit cell proliferation through cell cycle arrest.	↑p53	[65]

6.7. Additive or synergistic effect of SF with other phytochemicals and therapeutic agents

Activation of c-jun N-terminal kinase (JNK) induced apoptosis independent of caspases in HCT15 cells by treating of UA and 5-FU synergistically.UA increase autophagy by inducing the accumulation of LC3 and p62 levels with involvement of JNK pathway which determined by using nude mice xenograft with HCT15 cells. [66] UA synergistically use oxaliplatin on SW480, SW620, LoVo, RKO were used in vitro models of SW620 xenograft mouse model where UA inhibited proliferation and induced apoptosis and enhanced cytotoxicity. Down-regulation of Bcl-XL, Bcl-2, survivin, caspase-3, 8,9 activations and inhibition of KRAS expression and BRAF, MEK1/2, ERK1/2, p-38, JNK, AKT, IKKα, IkBα and p65 phosphorylation of MAPK, PI3/AKT, and NF-kB signaling pathways. UA decrease the burden of oxaliplatin effect on colon cancer cell. [67] Another combination of UA and oxaliplatin (Oxa) use to inhibit cell proliferation of RKO cells. Upregulation of caspase-3, caspase-8, and caspase-9 and Z-VAD-FMK, caspase inhibitor. Combination of UA and OXa activated caspase 3,8,9 and induced apoptosis and down regulated the expression of X linked inhibitor of apoptosis and survivin. [68] UA inhibit COX-2 in colon cancer cells. UA and paclitaxel combination use cytotoxicity and their dose and time dependent inhibited BGC-823 and SGC-7901 colon cancer cells. Western blot analysis seen the expression of a series of related proteins including COX-2, proliferation

cell nuclear antigen (PCNA), Bcl-2 and Bax upregulated. [69] UA and CPT-11 enhanced anti-tumorigenic activity based on down-regulation of the Upa/upar dependent MMP pathway down regulate. UA and OA exhibit protective effect towards normal cells. [70] UA and KA gives synergistic effect on HCT116 cell line. Decrease expression Level of NF-KB with radiation approved for UA and 2Gy pf radiation. UA lead radio sensitization of human colon tumor cells by NF-KB1 and CCND1 signaling pathways. [71] A sterically stabilized unilamellar nanocarrier vesicle (SSV) system used develop of UA structure and this combination targets MAPK pathway. There co-delivery vesicles enable their direct medical application, possibly overcoming the multidrug resistance effect. [72] DKC1 binds and stabilizes the mRNA of RP including RPL10A, RPL22L1, RPL34, RPS3, DKC1 depletion accelerate mRNA decay. DKC1 regulate RPs and interact with HRAS and suppress the RAS/RAF/MEK/ERK pathway. Pyrazofurin and trametinib combination synergistically restrains colon cancer cell growth in vitro and in vivo. [73]

In vivo studies

Ursolic acid (UA) applied to gemcitabine, AsPC-1, MIA PaCa-2, and Panc-28 cells in nude mice orthotopically. Cell proliferation, metastatic and angiogenic proteins and apoptosis are done by UA. 20μM UA and 200nM gemcitabine induced apoptosis and suppressed the expression of NF-kB- regulated proteins. These combination therapy decrease miR-29a closely linked with tumorigenesis. UA inhibit pancreatic tumors and colon cancer cell and sensitize to gemcitabine by suppressing inflammatory biomarkers linked to proliferation, invasion, angiogenesis and metastasis. [74] Activation of multiple intracellular signaling transduction cascades including STAT3, ERK, JNK and P38 pathways. In this mechanism complicated signaling network regulated by their pathways crosstalk. UA treated on HT29 cell line in xenograft mouse model in vitro and in vivo and investigate inhibition of cancer growth without apparent toxicity by alteration of critical target genes and colon cancer related signaling pathways. [75]Black raspberry extract contain UA and use in diet of mouse model 12 weeks feeding colon cancer cell growth response by 45% and 60% tumor multiplicity in Apc1638+/- mice and 50% Muc2-/- mice/. B catenin signaling pathway suppress and reduce chronic inflammation. [76] Polyphenol rich berry extract contains UA and applied on HeLa cell and Caco-2 cell with IC50 value 25-40 μg/mL. and inhibit cell growth and cell proliferation with antiproliferative activity. [77] UA treated on colon cancer cell with azocymethane and dextran sulfate sodium salt on BALB/c mouse model mRNA and miRNA expression divided on four groups. Scientist observed dysregulation of many pathways, upregulation of Wnt signaling pathways and downregulation of apoptosis protein. [78] Dried plum or prunes extract contain different polyphenol and UA were applied in diet on mouse model in four different diet groups. These findings saw that colon cancer cell do not die but also lower colon cancer risk [79].

Table 5: Effect of EA, SF, and UA on colon tumors cell line in animals

Phytochemical	Effect	Dose/duration	Route	Reference
EA	Pharmacokinetics andtoxicity on miRNA study		Diet	[28]
EA	Apoptosis, differentiation, and development		Diet	[29]
EA	Tumor invention, initiation and metastasis		Diet	[30]
	study.			
EA	Downregulation and upregulation of oncogenes.		Diet	[31]
EA	Inhibition of tumor growth		Diet	[32]
EA	Induced rat colon cell tumor	200 mg/kg/daily	Diet	[33]
SF	Induced hepatic hepcidin inflamationa nd reduce liver cancer risk.	2 μM, 24 Hrs	Diet	[51]
SF	Anticancer effect and nutritional intervention.	80 mg/kg, 8 days	Diet	[52]
SF	Decreased cell viability.	106.5 μM; 15 days	Intravenous	[53]
SF	Regulation of intestinal cell growth and death.	30 μM	Diet	[54]

International Journal of Clinical and Medical Case Reports

SF	Induced obesity associate colon cancer.	10 and 15 mg/kg, 8 weeks	Diet	[55]
SF	Anti-inflammatory effect	11.9 mg/kg/day; 25 days	Diet	[56]
UA	Inhibit cancer cell growth, suppression of cell proliferation, invasion, angiogenesis, metastasis.	250 mg/kg, 25mg/kg	Diet	[74]
UA	Anti-cancer activity	50 µM	Diet	[75]
UA	Cell proliferation	25 µM	Diet	[76]
UA	Tumor anti proliferation	25-40 µg	Diet	[77]
UA	Identify metabolic gene.		Diet	[78]
UA	Antioxidant activity	15 mg/kg	Diet	[79]

7. Future Directions And Conclusions

In the field of medication research, dietary phytochemicals earned safety for long-term use. Several polyphenols and herbal medications have been shown to inhibit the growth of colon cancer cells. Evidence suggests that EA, SF and UA are potential participants in the creation of a comprehensive approach for the management and variance of colon cancer cells. These dietary elements have been found to inhibit tumor cell development, induce apoptosis and stop the cell cycle, all of which have been shown to have anti colon cancer effects. In vitro models have been used in almost all investigations in agreement with the findings of the initial research. To validate their effectiveness, in vivo experiments with trustworthy animal models of colon cancer must be performed. The majority of the investigations have looked at particular compounds. The agent's potential as a sensitizer and potentiator of chemotherapeutic drugs has to be investigated further. In preclinical studies on EA, SF and UA as an anticancer medication for the prevention of colon cancer, attention must be paid to enhancing bioavailability. (Fig 1) Including synthetic analogs of these could improve bioavailability. Combinatorial treatment may also aid in the improvement of bioavailability. Additionally needed are epidemiological studies, clinical trials, and the assessment of safety profiles, the identification of novel target proteins and the routes through which they work. The in vivo and in vitro results taken into account in this study that EA, SF and UA could be useful in the prevention and treatment of colon cancer.

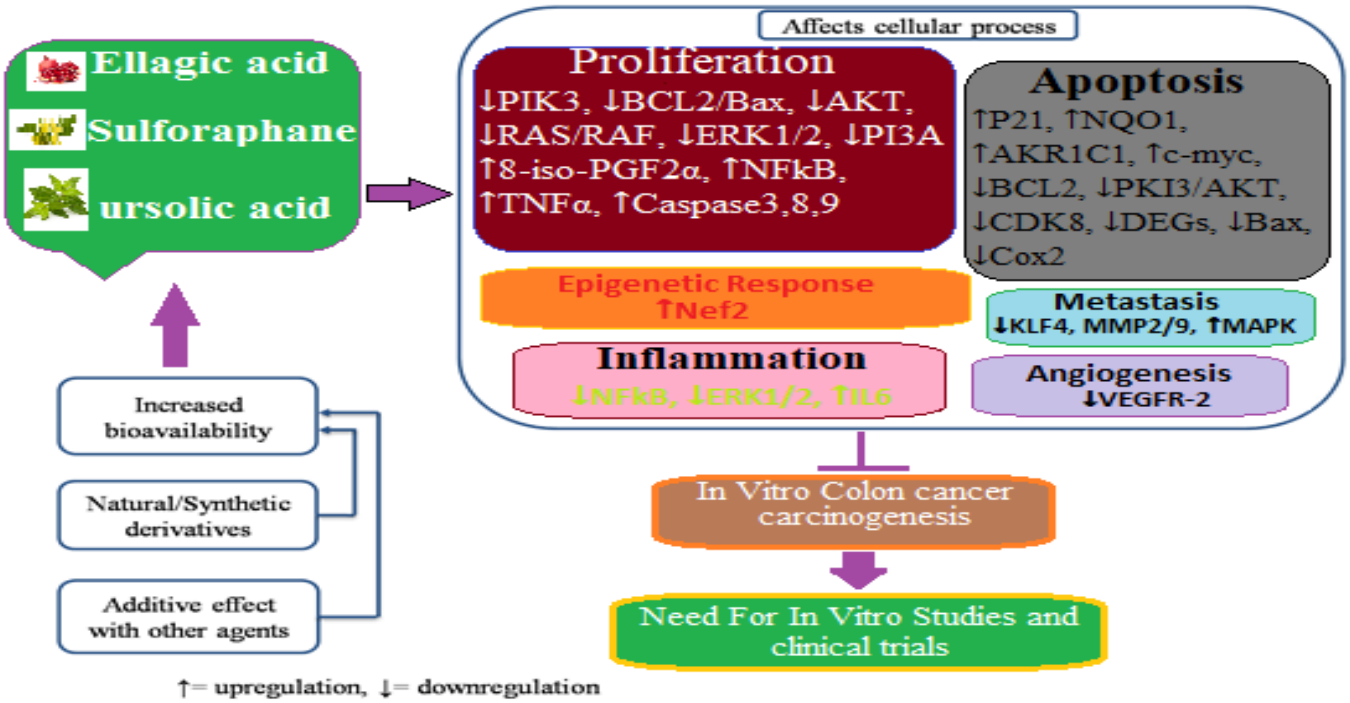


Figure 1. Schematic representation of the role of EA, SF, and UA in colon cancer. The figure also illustrates the future directions.

8. Acknowledgements

This Research article was originally written by Md. Sadikuj Jaman and Md. Rokibul Hasan Bhuiyan. This paper was reviewed and Edited by co-authors. Authors are grateful to all staff of Department of Biochemistry and Molecular Biology, University of Rajshahi 6205 and Department of Pharmacy, Veranda University, Rajshahi.

9. Contributions

The first draft of the manuscript was originally written by Md Sadikuj Jaman and Md Rokibul Hasan Bhuiyan and all authors commented on the manuscript. All authors contributed to the study conception and design. Table arrangement, Data collection and analysis, Figure design, Material preparation was done by Md. Sadikuj Jaman, Md. Maniruzzaman Sabina Akter, Md. Rokibul Hasan Bhuiyan All authors read and approved the final manuscript.

References

1. Md. Rokibul Hasan Bhuiyan, Md.Maniruzzaman Sabina Akter, Most. Humayra Binta Rashid, Md. Ehasanullah & Md.Sadikuj Jaman. Assessment of Antioxidant and Antineoplastic Activities Blumea Lacera (Burn. F) Leaves. Int Aca.J App Biomed Sci. 2022: 3(5); 1-10
2. Md Sadikujjaman, Md Abu Sayeed. "Ellagic Acid, Sulphoraphan, And Ursolic Acid In The Prevention And Therapy Of Breast Cancer: Current Evidence And Future Perspectives" Breast Cancer 2018; 25: 517. Https://Doi.Org/10.1007
3. Jaman Ms, Alam Ms, Rezwan Ms, Islam Mr, Husna Au And Sayeed Ma. Comparison of Total Antioxidant Activity between Fresh and Commercial Mango Juices Available In Bangladesh. Gsc Biological And Pharmaceutical Sciences. 2017; 1(2): 026-033.
4. aman S, Rezwan S, Alam S, Islam R, Husna A U, Sayeed S. Association Of Mean Platelet Volume And Platelet Distribution Width With Hba1c. Journal Of Endocrinology And Diabetes. 2017; 4(4): 1-6.
5. Jaman Ms, Rahaman Ms, Swarma Rr, Mahato J And Siddique Mae, Ayeshasiddika M."Diabetes And Red Blood Cell Parameters" Ann Clin Endocrinol Metabol.2018; 2: 001-00.
6. Núñez-Sánchez Ma, García-Villalba R, Monedero-Saiz T, Et Al. "Targeted Metabolomics Profiling Of Pomegranate Polyphenols and Urolithins in Plasma, Urine and Colon Tissues from Colorectal Cancer Patients". Mol Nutr Food Res. 2014; 58: 1199-1211.
7. Seeram Np, Aronson Wj, Zhang Y, Et Al. "Pomegranate Ellagitannin-Derived Metabolites Inhibit Prostate Cancer Growth and Localize To the Mouse Prostate Gland". J Agric Food Chem. 2007: 55: 7732–7737.
8. Zhang Y. "The Molecular Basis That Unifies The Metabolism, Cellular Uptake And Chemopreventive Activities Of Dietary Isothiocyanates" Carcinogenesis. 2012; 33: 2-9.
9. Md. Rokibul Hasan Bhuiyan, Md. Maniruzzaman, Sabina Akter, Sanzia Mehjabin, Md. Rakib Rased Rana, and Md. Sadikuj Jaman. Drug Promising Effect For Diabetic Mice Of CARICA PAPAYA Leaves. Euro J Pharmaceutical Research. 2022; 2(3). DOI: 10.24018/harma.2022.2.3.47
10. Gasper Av, Al-Janobi A, Smith Ja, Et Al. "Glutathione S-Transferase M1 Polymorphism And Metabolism Of Sulforaphane From Standard And High-Glucosinolate Broccoli" Am J Clin Nutr. 2005; 82: 1283-1291.
11. Veeranki Ol, Bhattacharya A, Marshall Jr, Zhang Y. "Organ-Specific Exposure and Response to Sulforaphane, A Key Chemopreventive Ingredient in Broccoli: Implications for Cancer Prevention" Br J Nutr. 2013; 109: 25-32.
12. Clarke Jd, Hsu A, Williams De, Et Al. "Metabolism And Tissue Distribution Of Sulforaphane In Nrf2 Knockout And Wild-Type Mice" Pharm Res. 2011; 28: 3171-3179.
13. Cornblatt Bs, Ye L, Dinkova-Kostova At, Et Al. "Preclinical And Clinical Evaluation Of Sulforaphane For Chemoprevention In The Breast" Carcinogenesis. 2007; 28: 1485-1490.
14. Chen H, Gao Y, Wang A, Zhou X, Zheng Y, Zhou J. "Evolution In Medicinal Chemistry Of Ursolic Acid Derivatives As Anticancer Agents" Eur J Med Chem. 2015A; 92: 648-655.
15. Liao Q, Yang W, Jia Y, Chen X, Gao Q, Bi K. "Lc-Ms Determination And Pharmacokinetic Studies Of Ursolic Acid In Rat Plasma After Administration Of The Traditional Chinese Medicinal Preparation Lu-Ying Extract" Yakugaku Zasshi. 2005; 125: 509-515.
16. Xia Y, Wei G, Si D, Liu C. "Quantitation Of Ursolic Acid In Human Plasma By Ultra-Performance Liquid Chromatography Tandem Mass Spectrometry And Its Pharmacokinetic Study" J Chromatogr B Analyt Technol Biomed Life Sci. 2011; 879: 219-224.
17. Jeong Saifujjaman M, Yi J, Lee S, Lee J. "Modeling For Mineral Redistribution Of Coal Blending During Pulverized Coal Combustion" International Mechanical Engineering Congress & Exposition, Imece. 2018-87834
18. Dario E. Iglesias, Eleonora Cremonini, Cesar G. Fraga And Patricia I. Oteiz. " Ellagic Acid Protects Caco-2 Cell Monolayers Against Inflammation-Induced Permeabilization" Free Radical Biology And Medicine. 2020; 152; 776-786.
19. Syed Umesalma , Ponnuraj Nagendraprabhu, Ganapasam Sudhandiran. "Ellagic Acid Inhibits Proliferation And Induced Apoptosis Via The Akt Signaling Pathway In Hct-15 Colon Adenocarcinoma Cells" Mol Cell Biochem. 2015; 399(1-2): 303-13. Doi: 10.1007/S11010-014-2257-2.
20. Verhoeckx K, Cotter P, López-Expósito I, Kleiveland C, Lea T, Mackie A, Requena T, et al. "The Impact Of Food Bioactives On Health - In Vitro And Ex Vivo Models" Editors. Cham (Ch). 2015.
21. Yang Fang, Hong Zhou, Jian-Fu Xia, et al. "Ellagic Acid Regulates Wnt/B-Catenin Signaling Pathway And Cdk8 In Hct 116 And Ht 29 Colon Cancer Cells". Bangladesh Journal Of Pharmacology. 2015; 10: 47-57, Doi: 10.3329/Bjp.V10i1.21068
22. Zhao J, Li G, Wei J, Dang S, Yu X, Ding L, et al. "Ellagic Acid Induces Cell Cycle Arrest And Apoptosis Via The Tgf-B1/Smad3 Signaling Pathway In Human Colon Cancer Hct-116 Cells." Oncol

Rep. 2020; 44(2): 768-776. Doi:10.3892/Or.2020.7617

23. Mouat MF, Kolli K, Orlando R. et al. "The Effects Of Quercetin On Sw480 Human Colon Carcinoma Cells: A Proteomic Study" Nutr J. 2005; 4; 11. Https://Doi.Org/10.1186/1475-2891-4-11
24. Cota D, Patil D. Antibacterial Potential of Ellagic Acid and Gallic Acid Against Ibd Bacterial Isolates and Cytotoxicity Against Colorectal Cancer. Nat Prod Res. 2022; 151-5. Doi: 10.1080/14786419.2022.2111560
25. Shi L, Gao X, Li X, Et Al. "Ellagic Acid Enhances The Efficacy Of Pi3k Inhibitor Gdc-0941 In Breast Cancer Cells" Curr Mol Med. 2015; 15: 478-486.
26. Rocha A, Wang L, Penichet M, Martins-Green M. "Pomegranate Juice And Specific Components Inhibit Cell And Molecular Processes Critical For Metastasis Of Breast Cancer." Breast Cancer Res Treat. 2012; 136(3): 647-58.
27. Shirode Ab, Bharali Dj, Nallanthighal S, Coon Jk, Mousa Sa, Reliene R. "Nanoencapsulation Of Pomegranate Bioactive Compounds For Breast Cancer Chemoprevention." Int J Nanomedicine. 2015; 10: 475-484.
28. Schetter Aj, Okayama H, Harris Cc. "The Role Of Micrornas In Colorectal Cancer." Cancer J. 2012; 18(3): 244-52. Doi: 10.1097/Ppo.0B013E318258B78F..
29. Daniel W. Rosenberg, Charles Giardina, Takuji Tanaka. "Mouse Models For The Study Of Colon Carcinogenesis." Carcinogenesis, 2009; 30(2); 183-196. Https://Doi.Org/10.1093/Carcin/Bgn267
30. Slaby O, Svoboda M, Michalek J. et al. "Micrornas In Colorectal Cancer: Translation Of Molecular Biology Into Clinical Application." Mol Cancer. 2009; 8; 102 Https://Doi.Org/10.1186/1476-4598-8-102
31. Rosa Hernández, Ester Sánchez-Jiménez, Consolación Melguizo, Jose Prados And Ana Rosa Rama. "Downregulated Micrornas In The Colorectal Cancer: Diagnostic And Therapeutic Perspectives" Bmb Reports. 2018; 51(11): 563-571 Https://Doi.Org/10.5483/Bmbrep.2018.51.11.116
32. Munagala R, Aqil F, Vadhanam MV & Gupta RC. Microrna 'Signature' During Estrogen-Mediated Mammary Carcinogenesis And Its Reversal By Ellagic Acid Intervention. Cancer Letters. 2013; 339(2): 175-184.
33. Parasramka Ma, Dashwood Wm, Wang R, Saeed Hh, Williams De, Ho E, Dashwood Rh. "A Role For Low-Abundance Mirnas In Colon Cancer: The Mir-206/Krüppel-Like Factor 4 (Klf4) Axis" Clin Epigenetics. 2012; 4(1): 16. Doi: 10.1186/1868-7083-4-16
34. Manasvi S. Shah, Scott L. Schwartz, Chen Zhao, Laurie A. Davidson, Beiyan Zhou, Joanne R. Lupton, Ivan Ivanov And Robert S. Chapkin. "Integrated Microrna And Mrna Expression Profiling In A Rat Coloncarcinogenesis Model: Effect Of A Chemo-Protective Diet " Physiol Genomics. 2011; 43: 640-654. Doi:10.1152/Physiolgenomics.00213.2010.
35. E Jeong K, Saifujjaman M, Aryal S, Tamang S, Lee S, Lee. Modeling For Blended Coal Combustion And Its Impact On Ash Deposition In Full-Scale Post-Boiler Equipment In A Supercritical Pulverized Coal-Fired Power Plant. 12TH Asia-Pacific Conference On Combustion. 2019.
36. Daddiouaissa D, Amid A, Abdullah Sani Ms, Elnour Aam. "Evaluation Of Metabolomics Behavior Of Human Colon Cancer Ht29 Cell Lines Treated With Ionic Liquid Graviola Fruit Pulp Extract." J Ethnopharmacol. 2021; 24: 270:113813. Doi: 10.1016/J.Jep.2021.113813.
37. Zhao X, Feng P, He W, Du X, Chen C, Suo L, Liang M, Zhang N, Na A, Zhang Y. "The Prevention And Inhibition Effect Of Anthocyanins On Colorectal Cancer." Curr Pharm Des. 2019; 25(46): 4919-4927. Doi: 10.2174/1381612825666191212105145.
38. Guo Y, Liu H, Xiao H, Yuan M, Liu Y, Sedlařík V, Chin Wc, Liu J, Guo L, Li C. "Self-Assembled Camptothecin Derivatives - Curcuminoids Conjugate For Combinatorial Chemo-Photodynamic Therapy To Enhance Anti-Tumor Efficacy." J Photochem Photobiol B. 2021; 215: 112124. Doi: 10.1016/J.Jphotobiol.2021.112124.
39. Lu W, Jia G, Meng X, Zhao C, Zhang L, Ren Y, Pan H, Ni Y. Beta-Catenin Mediates The Apoptosis Induction Effect Of Celastrol In Ht29 Cells. Life Sci. 2012; 17; 91(7-8): 279-83. Doi: 10.1016/J.Lfs.2012.07.032.
40. Ramos Aa, Pedro D, Collins Ar, Pereira-Wilson C. "Protection By Salvia Extracts Against Oxidative And Alkylation Damage To Dna In Human Hct15 And Co115 Cells." J Toxicol Environ Health A. 2012; 75(13-15): 765-75. Doi: 10.1080/15287394.2012.689804.
41. Cristina P.R. Xavier, Cristina Pereira-Wilson (2016) "Medicinal Plants Of The Genuses Salvia And Hypericum Are Sources Of Anticolon Cancer Compounds: Effects On Pi3k/Akt And Map Kinases Pathways",Pharmanutrition. 2016; 4(2): 112-122. Https://Doi.Org/10.1016/J.Phanu.2015.11.002.
42. R Tundis, D Iacopetta, MS Sinicropi, M Bonesi, M Leporini, NG. Passalacqua, J Ceramella, F Menichini, MR Loizzo. "Assessment Of Antioxidant, Antitumor And Pro-Apoptotic Effects Of Salvia Fruticosa Mill. Subsp. Thomasii (Lacaita) Brullo, Guglielmo, Pavone & Terrasi (Lamiaceae)"Food And Chemical Toxicology. 2017; 106(A): 155-164. Https://Doi.Org/10.1016/J.Fct.2017.05.040.
43. Jang Hy, Kim Dh, Lee Hj, Kim Wd, Kim Sy, Hwang Jj, Lee Sj, Moon Dh. "Schedule-Dependent Synergistic Effects Of 5-Fluorouracil And Selumetinib In Kras Or Braf Mutant Colon Cancer Models." Biochem Pharmacol. 2019; 160: 110-120. Doi: 10.1016/J.Bcp.2018.12.017.
44. Shimao Y, Nabeshima K, Inoue T, Koono M. (1999) "Role Of Fibroblasts In Hgf/Sf-Induced Cohort Migration Of Human Colorectal Carcinoma Cells: Fibroblasts Stimulate Migration Associated With Increased Fibronectin Production Via Upregulated Tgf-Beta1." Int J Cancer. 30;82(3):449-58. Doi: 10.1002/(Sici)1097-0215(19990730)82:3<449::Aid-Ijc20>3.0.Co;2-H. Pmid: 10399964.
45. He S, Guo Y, Zhao J, Xu X, Wang N, Liu Q. (2020) "Ferulic Acid Ameliorates Lipopolysaccharide-Induced Barrier Dysfunction Via Microrna-200C-3P-Mediated Activation Of Pi3k/Akt Pathway In Caco-2 Cells." Front Pharmacol. 3;11:376. Doi: 10.3389/Fphar.2020.00376. Pmid: 32308620; Pmcid: Pmc7145943.
46. Kewei Ren, Wenzhe Zhang, Gang Wu, Jianzhuang Ren, Huibin Lu, Zongming Li, Xinwei Han, (2016) "Synergistic Anti-Cancer Effects Of Galangin And Berberine Through Apoptosis Induction And Proliferation Inhibition In Oesophageal Carcinoma Cells",

Biomedicine & Pharmacotherapy, Volume 84, Pages 1748-1759, Issn 0753-3322, Https://Doi.Org/10.1016/J.Biopha.2016.10.111.

47. Chao Huang, Keming Xiang, Bingjun Liang, Weixuan Huang, Fanjun Zhang, Yuwan Shao, Xiulian Wang, Haosheng Liu, Weizeng Shen, (2020) "Combination Of Evodiamine With Berberine Reveals A Regulatory Effect On The Phenotypic Transition Of Colon Epithelial Cells Induced By Ccd-18co", Chinese Medical Sciences Journal, Volume 35, Issue 3, Pages 195-206, Issn 1001-9294, Https://Doi.Org/10.24920/003670.
48. Hye Yeon Jang, Do Hyung Kim, Haeng Jung Lee, Won Dong Kim, Seog-Young Kim, Jung Jin Hwang, Seung Jin Lee, Dae Hyuk Moon, (2019) "Schedule-Dependent Synergistic Effects Of 5-Fluorouracil And Selumetinib In Kras Or Braf Mutant Colon Cancer Models", Biochemical Pharmacology, Volume 160, Pages 110-120, Issn 0006-2952, Https://Doi.Org/10.1016/J.Bcp.2018.12.017.
49. Muhammad Asif, Ashwaq H.S. Yehya, Saad Sabbar Dahham, Shazmin Kithur Mohamed, Armaghan Shafaei, Mohammed Oday Ezzat, Aman Shah Abdul Majid, Chern Ein Oon, Amin Malik Shah Abdul Majid, (2019) "Establishment Of In Vitro And In Vivo Anti-Colon Cancer Efficacy Of Essential Oils Containing Oleo-Gum Resin Extract Of Mesua Ferrea", Biomedicine & Pharmacotherapy, Volume 109, Pages 1620-1629, Issn 0753-3322, Https://Doi.Org/10.1016/J.Biopha.2018.10.127.
50. Ala'a Al-Bakheit, Luay Abu-Qatouseh (2020) "Sulforaphane From Broccoli Attenuates Inflammatory Hepcidin By Reducing Il-6 Secretion In Human Hepg2 Cells",Journal Of Functional Foods,Volume 75,104210,Issn 1756-4646,Https://Doi.Org/10.1016/J.Jff.2020.104210.
51. Zhongyue Ren, Shufang Chen, Huihui Lv, Lingling Peng, Wanyu Yang, Jiahui Chen, Zhihua Wu, Cuixiang Wan, (2022) "Effect Of Bifidobacterium Animalis Subsp. Lactis Sf On Enhancing The Tumor Suppression Of Irinotecan By Regulating The Intestinal Flora." Pharmacological Research,Volume 184,106406,Issn 1043-6618,Https://Doi.Org/10.1016/J.Phrs.2022.106406.
52. Evans Jp, Winiarski Bk, Sutton Pa, Jones Rp, Ressel L, Duckworth Ca, Pritchard Dm, Lin Zx, Fretwell Vl, Tweedle Em, Costello E, Goldring Ce, Copple Im, Park Bk, Palmer Dh, Kitteringham Nr. (2018) "The Nrf2 Inhibitor Brusatol Is A Potent Antitumour Agent In An Orthotopic Mouse Model Of Colorectal Cancer." Oncotarget. 5;9(43):27104-27116. Doi: 10.18632/Oncotarget.25497
53. Geraldine Parnaud, Pengfei Li, Georges Cassar, Patrick Rouimi, Jacques Tulliez, Lydie Combaret & Laurence Gamet-Payrastre(2004)Mechanism Of Sulforaphane-Induced Cell Cycle Arrest And Apoptosis In Human Colon Cancer Cells,Nutrition And Cancer,48:2,198-206,Doi: 10.1207/S15327914nc4802_10
54. A.M. Eskin, J. Raju, R.P. Bird (2007) "Novel Mucilage Fraction Of Sinapis Alba L. (Mustard) Reduces Azoxymethane-Induced Colonic Aberrant Crypt Foci Formation In F344 And Zucker Obese Rats",Phytomedicine,Volume 14, Issues 7–8, Pages 479-485,Issn 09447113,Https://Doi.Org/10.1016/J.Phymed.2006.09.016.
55. Marta Zielińska, Urszula Lewandowska, Anna Podsędek, Adam I. Cygankiewicz, Damian Jacenik, Maciej Sałaga, Radzisław Kordek, Wanda M. Krajewska, Jakub Fichna (2015) "Orally Available Extract From Brassica Oleracea Var. Capitata Rubra Attenuates Experimental Colitis In Mouse Models Of Inflammatory Bowel Diseases" Journal Of Functional Foods,Volume 17, Pages 587-599,Issn 1756-4646,Https://Doi.Org/10.1016/J.Jff.2015.05.046.
56. Saifujjaman, M, Jeong, K, & Lee, S(2018). "Modeling For Mineral Redistribution Of Coal Blending During Pulverized Coal Combustion." Proceedings Of The Asme 2018 International Mechanical Engineering Congress And Exposition. Volume 8a: Heat Transfer And Thermal Engineering, V08at10a011. Asme. Https://Doi.Org/10.1115/Imece2018-87834
57. Alice A. Ramos, Cristina Pereira-Wilson, Andrew R. Collins (2010) "Protective Effects Of Ursolic Acid And Luteolin Against Oxidative Dna Damage Include Enhancement Of Dna Repair In Caco-2 Cells", Mutation Research/Fundamental And Molecular Mechanisms Of Mutagenesis,Volume 692, Issues 1–2, Pages 6-11,Issn 0027-5107,Https://Doi.Org/10.1016/J.Mrfmmm.2010.07.004.
58. Zhiyi Qiang, Zhong Ye, Cathy Hauck, Patricia A. Murphy, Joe-Ann Mccoy, Mark P. Widrlechner, Manju B. Reddy, Suzanne Hendrich (2011) "Permeability Of Rosmarinic Acid In Prunella Vulgaris And Ursolic Acid In Salvia Officinalis Extracts Across Caco-2 Cell Monolayers",Journal Of Ethnopharmacology, Volume 137, Issue 3, Pages 1107-1112, Issn 0378-8741, Https://Doi.Org/10.1016/J.Jep.2011.07.037.
59. El-Wetidy, M.S., Ahmad, R., Rady, I. Et Al. (2021) "Urolithin A Induces Cell Cycle Arrest And Apoptosis By Inhibiting Bcl-2, Increasing P53-P21 Proteins And Reactive Oxygen Species Production In Colorectal Cancer Cells." Cell Stress And Chaperones26, 473–493 Https://Doi.Org/10.1007/S12192-020-01189-8
60. González-Sarrías, A., Espín, J.-C., Tomás-Barberán, F.A. And García-Conesa, M.-T. (2009) "Gene Expression, Cell Cycle Arrest And Mapk Signalling Regulation In Caco-2 Cells Exposed To Ellagic Acid And Its Metabolites, Urolithins." Mol. Nutr. Food Res., 53: 686-698. Https://Doi.Org/10.1002/Mnfr.200800150
61. Youness Limami, Aline Pinon, David Yannick Leger, Yoanne Mousseau, Jeanne Cook-Moreau, Jean-Louis Beneytout, Christiane Delage, Bertrand Liagre, Alain Simon (2011) "Ht-29 Colorectal Cancer Cells Undergoing Apoptosis Overexpress Cox-2 To Delay Ursolic Acid-Induced Cell Death",Biochimie,Volume 93, Issue 4,Pages 749-757,Issn 0300-9084,Https://Doi.Org/10.1016/J.Biochi.2011.01.003.
62. Xuemei Wang, Fan Zhang, Ling Yang, Ying Mei, Hai Long, Xiaowen Zhang, Jialing Zhang, Undefined Qimuge-Suyila, Xiulan Su, (2011) "Ursolic Acid Inhibits Proliferation And Induces Apoptosis Of Cancer Cells In Vitro And In Vivo", Biomed Research International, Vol. 2011, Article Id 419343, 8 Pages, Https://Doi.Org/10.1155/2011/419343
63. Cristina P.R. Xavier, Cristovao F. Lima, Ana Preto, Raquel Seruca, Manuel Fernandes-Ferreira, Cristina Pereira-Wilson (2009) "Luteolin, Quercetin And Ursolic Acid Are Potent Inhibitors Of Proliferation And Inducers Of Apoptosis In Both Kras And Braf

Mutated Human Colorectal Cancer Cells",Cancer Letters,Volume 281, Issue 2, Pages 162-170,Issn 0304-3835,Https://Doi.Org/10.1016/J.Canlet.2009.02.041.

64. Li J, Guo Wj, Yang Qy (2002) "Effects Of Ursolic Acid And Oleanolic Acid On Human Colon Carcinoma Cell Line Hct15." World J Gastroenterol. 8(3):493-5. Doi: 10.3748/Wjg.V8.I3.493. Pmid: 12046077; Pmcid: Pmc4656428.
65. Cristina P.R. Xavier, Cristovao F. Lima, Dalila F.N. Pedro, Jonathan M. Wilson, Karsten Kristiansen, Cristina Pereira-Wilson (2013) "Ursolic Acid Induces Cell Death And Modulates Autophagy Through Jnk Pathway In Apoptosis-Resistant Colorectal Cancer Cells",The Journal Of Nutritional Biochemistry,Volume 24, Issue 4,Pages 706-712,Issn 0955-2863,Https://Doi.Org/10.1016/J.Jnutbio.2012.04.004.
66. Shan, J., Xuan, Y., Zhang, Q. Et Al. (2016) "Ursolic Acid Synergistically Enhances The Therapeutic Effects Of Oxaliplatin In Colorectal Cancer." Protein Cell7, 571–585 Https://Doi.Org/10.1007/S13238-016-0295-0
67. Zheng, Jia -Lu ; Wang, Shuang-Shuang ; Shen, Ke-Ping ; Huang, Xiao-Wei; Li, Miao; Chen, Lei; Peng, Xiao; An, Hong-Mei; Hu, Bing (2020) "Ursolic Acid Potentiated Oxaliplatin To Induce Apoptosis In Colorectal Cancer Rko Cells" Die Pharmazie An International Journal Of Pharmaceutical Sciences, Volume 75, Pp. 246-249(4) Doi: Https://Doi.Org/10.1691/Ph.2020.0417
68. Xu X, Zhu Gq, Zhang K, Zhou Yc, Li Xl, Xu W, Zhang H, Shao Y, Zhang Zy, Sun Wh. (2017) "Cyclooxygenase-2 Mediated Synergistic Effect Of Ursolic Acid In Combination With Paclitaxel Against Human Gastric Carcinoma." Oncotarget. 6;8(54):92770-92777. Doi: 10.18632/Oncotarget.21576. Pmid: 29190954; Pmcid: Pmc5696220.
69. Mateusz Piet, Roman Paduch (2022) "Ursolic And Oleanolic Acids In Combination Therapy Inhibit Migration Of Colon Cancer Cells Through Down-Regulation Of The Upa/Upar-Dependent Mmps Pathway",Chemico-Biological Interactions,Volume 368, 110202,Https://Doi.Org/10.1016/J.Cbi.2022.110202.
70. Maede Hasan Abdali, Saeid Afshar, Abdolazim Sedighi Pashaki, Dara Dastan, Mohammad Hadi Gholami, Roghayeh Mahmoudi, Massoud Saidijam, (2020) "Investigating The Effect Of Radiosensitizer For Ursolic Acid And Kamolonol Acetate On Hct-116 Cell Line",Bioorganic & Medicinal Chemistry,Volume 28, Issue 1, 115152,Issn 0968-0896,Https://Doi.Org/10.1016/J.Bmc.2019.115152.
71. Lőrincz, J. Mihály, A. Wacha, Cs. Németh, B. Besztercei, P. Gyulavári, Z. Varga, I. Peták, A. Bóta (2021) "Combination Of Multifunctional Ursolic Acid With Kinase Inhibitors For Anti-Cancer Drug Carrier Vesicles",Materials Science And Engineering: C,Volume 131,112481,Issn 0928-4931,Https://Doi.Org/10.1016/J.Msec.2021.112481.
72. Meiping Chang, Steven Huhn, Luke Nelson, Michael Betenbaugh, Zhimei Du (2022) "Significant Impact Of Mtorc1 And Atf4 Pathways In Cho Cell Recombinant Protein Production Induced By Cdk4/6 Inhibitor" Biotechnology And Bioengineering, 10.1002/Bit.28050, 119, 5, (1189-1206)
73. Prasad S, Yadav Vr, Sung B, Gupta Sc, Tyagi Ak, Aggarwal Bb. (2016) "Ursolic Acid Inhibits The Growth Of Human Pancreatic Cancer And Enhances The Antitumor Potential Of Gemcitabine In An Orthotopic Mouse Model Through Suppression Of The Inflammatory Microenvironment." Oncotarget. 15;7(11):13182-96. Doi: 10.18632/Oncotarget.7537. Pmid: 26909608; Pmcid: Pmc4914350.
74 Jiumao Lin, Youqin Chen, Lihui Wei, Aling Shen, Thomas J. Sferra, Zhenfeng Hong, Jun Peng. (2013) "Ursolic Acid Promotes Colorectal Cancer Cell Apoptosis And Inhibits Cell Proliferation Via Modulation Of Multiple Signaling Pathways" International Journal Of Oncology, Pages: 1235-1243 Https://Doi.Org/10.3892/Ijo.2013.2040
75. Xiuli Bi, Wenfeng Fang, Li-Shu Wang, Gary D. Stoner, Wancai Yang (2010) "Black Raspberries Inhibit Intestinal Tumorigenesis In Apc1638+/− And Muc2−/− Mouse Models Of Colorectal Cancer." Cancer Prev Res (Phila) 3 (11): 1443–1450. Https://Doi.Org/10.1158/1940-6207.Capr-10-0124
76. Gordon J. Mcdougall, Heather A. Ross, Magnus Ikeji, Derek Stewart. (2008) "Berry Extracts Exert Different Antiproliferative Effects Against Cervical And Colon Cancer Cells Grown In Vitro" J. Agric. Food Chem. 56, 9, 3016–3023 Https://Doi.Org/10.1021/Jf073469n
77. Yuyan Gao, Xin Li, Ming Yang, Qi Zhao, Xiaolong Liu, Guangyu Wang, Xiaolin Lu, Qi Wu, Jin Wu, Yanmei Yang, Yue Yang, Yanqiao Zhang (2013) "Colitis-Accelerated Colorectal Cancer And Metabolic Dysregulation In A Mouse Model." Carcinogenesis, Volume 34, Issue 8, Pages 1861–1869, Https://Doi.Org/10.1093/Carcin/Bgt135
78. Yuqing Yang & Daniel D. Gallaher.(2005) "Effect Of Dried Plums On Colon Cancer Risk Factors In Rats" Nutrition And Cancer,53:1,117-125,Doi: 10.1207/S15327914nc5301_14
79 Maria Trakakaren F Chamberskaren F Chamberselizabeth K Lundelizabeth K Lundrichard Mithenrichard Mithen. " Involvement Of Klf4 In Sulforaphane- And Iberin-Mediated Induction Of P21waf1/Cip1 ." Nutrition And Cancer. 2009; 61(1): 137-45 Doi: 10.1080/01635580802348641