Journal of Pharmacognosy and Phytochemistry

Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
www.phytojournal.com
JPP 2022; 11(2): 229-246
Received: 16-01-2022
Accepted: 21-02-2022

Senthil Kumar Raju
Department of Pharmaceutical Chemistry, Swamy Vivekanandha College of Pharmacy, Tiruchengode, Tamil Nadu, India

Praveen Sekar
Department of Pharmaceutical Chemistry, Swamy Vivekanandha College of Pharmacy, Tiruchengode, Tamil Nadu, India

Shridharshini Kumar
Department of Pharmaceutical Chemistry, Swamy Vivekanandha College of Pharmacy, Tiruchengode, Tamil Nadu, India

Maruthamuthu Murugesan
Department of Pharmaceutical Chemistry, Swamy Vivekanandha College of Pharmacy, Tiruchengode, Tamil Nadu, India

Mohanapriya Karthikeyan
Department of Pharmaceutical Chemistry, Swamy Vivekanandha College of Pharmacy, Tiruchengode, Tamil Nadu, India

Anjana Elampulakkadu
Department of Pharmaceutical Chemistry, Swamy Vivekanandha College of Pharmacy, Tiruchengode, Tamil Nadu, India

Corresponding Author:
Senthil Kumar Raju
Department of Pharmaceutical Chemistry, Swamy Vivekanandha College of Pharmacy, Tiruchengode, Tamil Nadu, India

Plant secondary metabolites for the prevention and treatment of colorectal cancer: A review

Senthil Kumar Raju, Praveen Sekar, Shridharshini Kumar, Maruthamuthu Murugesan, Mohanapriya Karthikeyan and Anjana Elampulakkadu

DOI: https://doi.org/10.22271/phyto.2022.v11.i2c.14390

Abstract
Colorectal cancer is becoming more common and deadly in both men and women nowadays. Although various treatment interventions are available including chemotherapy, surgery, radiation therapy and hormonal therapy, they are associated with some harmful effects. To avoid the risk factors associated with these therapies, natural products could be used as one of the most promising candidates for colorectal cancer. The natural products and their dietary supplements demonstrated stronger potential against various colorectal cancer cells. Flavonoids, phenolics, terpenoids, saponins, quinones, alkaloids, and other secondary metabolites are among the bioactive substances found in dietary supplements. These dietary phytochemicals exhibited strong and potent cytotoxicity against colorectal cancer cells which indicated their ability as chemopreventive agents. Both intrinsic and extrinsic routes were used to trigger apoptosis by the phytochemical substances. Phytochemicals influenced the cell cycle regulation, oncogenes, tumor markers and induced apoptosis by modulating tumor-suppressive miRNAs, affecting the cell signaling pathways, upregulating apoptotic inducers with the downregulation of anti-apoptotic proteins and factors. Thus, in this review, we addressed the sources and mechanism of various isolated phytochemicals as anti-colorectal cancer agents.

Keywords: Colorectal cancer, isolated phytochemicals, dietary supplements, apoptosis, signaling pathways

1. Introduction
Cancer is one of the major public health issues and according to World Health Organization (WHO); cancer is the leading cause of death worldwide before 70 years of age. Colorectal cancer is the second most frequent cancer and the fourth leading cause of cancer-related death among all malignancies [1-4]. Approximately, 10% of the annually diagnosed cancers were found to be colorectal cancer and common among men and women. Compared to the men, about 25% lesser mortality were found among women and predicted to have 2.5 million new cases in 2035. The exact reason for these increasing cases was not exactly understood, although lifestyle changes, genetic factors, environmental conditions and obesity may have some contributions [5].

Based on the GLOBOCAN, in 2021 colorectal cancer was found to be third in incidence and second in mortality rate. i.e., more than 1.9 million cases with 935000 deaths have occurred. It was found to be increasing in the future with new cases due to the modifications in lifestyle and diet. Colorectal cancer has been linked to a lack of physical exercise, high body weight, and other risk factors. 9.4% of deaths have occurred among 10% of cases with colorectal cancer. Due to the growth of population and increased risk factors, about 28.4 million new cases were estimated to be occurred in 2040, worldwide i.e., about 47% increased than 2020. The mortality rate of colorectal cancer increases parallelly with the incidence rates [2]. Due to the secondary additional risk factors like smoking, high alcohol consumption, etc. the incidence rates of colorectal cancer got increased and the usage of chemotherapeutic agents for the treatment was increased. However, traditional chemotherapy has been linked to increased toxicity and undesired side effects. Specifically, cisplatin, a stronger chemotherapeutic drug, is linked to nephrotoxicity, hepatotoxicity and cardiotoxicity [6, 7].

Like these types of side effects produced by cancer chemotherapy, the enormous drawbacks were produced by using surgery, radiotherapy, hormonal therapy and other newer targeted therapies. Dysesthesias and renal dysfunction were caused by administering irinotecan. The combination of irinotecan with 5-fluorouracil causes severe adverse effects like nausea, stomatitis, diarrhea, vomiting, mucositis, headache, skin pruritis, myelosuppression, cardiotoxicity, anxiety and neutropenia.

The gastrointestinal problems, urinary incontinence, sexual dysfunction and sensory neuropathy were also observed on the long-term treatment using chemotherapeutic agents and others [8, 9]. Thus, there is a need to design and develop a new class of compounds with less or without toxicity along with high efficiency to replace the conventional synthetic agents. The plants had the wide ability to treat diseases and these types of medicinal plants served as drug candidates with greater potential. The inclusion of their bioactive components resulted in improved and more effective efficacy against a variety of ailments [10, 11].

One of the novel approaches to develop anticancer agents was found to be the use of herbal medicine. In the 1950s, the vinca alkaloids were discovered and there is the growth and development of various plant-derived anticancer agents like paclitaxel. Thus, the plants and their active phytoconstituents were used from ancient days either directly from plants or by means of chemically modified phytoproducts [12]. The plant-derived phytochemicals from the vegetables and fruits enriched in the diet exhibited their potential against various types of cancers. Phytoconstituents from plants, such as phenolics, flavonoids, terpenoids, alkaloids, glycosides, steroids, saponins, quinones, secondary metabolites and others have shown to have a significant impact on carcinogenesis. The phytochemicals regulated the cellular mechanisms effectively with better cytotoxic potential. Plants or isolated substances that were high in phenolic groups have stronger anticancer, antioxidant, anti-inflammatory, and antibacterial properties [13-15]. Among the various phytoconstituents, bioactive polyphenolic compounds are important for colorectal carcinogenesis. It includes flavanones, flavonoids, isoflavonoids, terpenoids, capsanosides, catechins, etc. The plant extracts and isolated compounds were found to most important chemopreventive agents and also possess various biological activities. For a better understanding, polyisoprenylated benzophenones, a naturally occurring molecule, possessed anticancer, antiviral, antioxidant, and anti-inflammatory effects [16, 17].

The phytochemicals present in the plant extracts promote programmed cell death with the ROS and RNS accumulation, significant pro-apoptotic, necroptotic or autophagy, cell cycle arrest, DNA repair and metastasis. The apoptosis is especially due to the polyphenolic compounds which were mediated through multiple mechanisms, *viz*., activating signaling cascades, inflammatory deactivation, modification of cell cycle pathways and apoptotic proteins regulation [18, 19]. The activity and apoptosis were achieved by damaging DNA, regulating gene transcription through Wnt signaling pathway [20], Wnt/β-catenin signaling pathway [21], formation of autophagosomes [22], p62/SQSTM1 intracellular signaling i.e., sustained p62/SQSTM1 is sufficient to promote tumorigenesis, nuclear factor-κB (NF- κB) regulation, gene expression [23], Phosphatidylinositol 3-kinase (PI3K) – serine/threonine kinase (Akt), PI3K/Akt/mTOR signaling pathway [24], calcineurin-NFAT pathway [25], extracellular signal-regulated kinase signaling [26], Cdc25c-Cdc2-Cyclin B pathway [27], STAT3 signaling pathway [28] and nuclear factor-erythroid 2 p45-related factor 2 (Nrf2) signaling [29]. The PRL-3, CLIC4, BGN, THBS2 and TDP2 are the targets associated with colorectal cancer [30, 31]. The serine-threonine kinase, glycogen synthase kinase 3β (GSK3β), protease-activated receptor-2 (PAR2)-simulated colonospheres, a decrease of Ki-67 expression, BMP-2, β-catenin, jagged 1 and LGR-5 played a crucial role in tumor survival and proliferation [32, 33].

The literature search for this review was steered on PubMed, Embase, Science Direct and Google Scholar core databases from the time period between 2016 to 2021. The keywords used for search strategy include cancer, colorectal cancer, isolated phytoconstituents, plant extracts and medicinal plants. By collecting the kinds of literature by using these keywords individually or by combination, the collected articles were scrutinized based on the title and abstract of each article and excluded the irrelevant articles. Thus, in this review, we focused on the various isolated phytochemicals used against colorectal cancer along with their biological source and various signaling pathways involved in apoptosis.

2. Phytochemicals against colorectal cancer

2.1 Flavonoids

Flavonoids are one of the important phytochemical constituents which possessed better pharmacological activity on cancer cells. The isolated flavonoid isoorientin showed the activity in both dose and time-dependent manner against HT29 colorectal cancer cells. Apoptosis is one of the major parts of oncology, thus flavonoids induced apoptosis through cell cycle arresting and also by regulating apoptotic proteins [34]. The compound furawanin A is the flavonoid isolated from *Millettia pachycarpa* which increased the cell cycle arresting at G_1/G_0 phase against HCT116 and LOVO colorectal cancer cells. It also suppressed the cell migration and invasion capability of colorectal cells [35]. Flavonoids promoted DNA damage and cell cycle arrest. The compounds induced apoptosis through various signaling pathways such as the Wnt signaling pathway, NFκB pathway and telomerase survival pathway [36, 37].

The various isolated flavonoids along with their sources, structures and mechanism are given in Table 1 and Figure 1.

Table 1: Sources and mechanisms of isolated flavonoids

Phytochemicals (Compound number)	Source	Mechanism	Reference
Butrin (1)	*Butea monosperma*	The apoptotic factors such as Bax, Bak, caspase was increased on the mitochondrial pathway and the accumulation of ROS induced apoptosis. It also downregulated GSK3β, cyclin D1, SIRT1 and AURKB at the mRNA level through the Wnt signaling pathway. The downregulation induced apoptosis by cell cycle arresting at G_1/S phase	[3]
Isorhamnetin 3,7-di-O-glucoside (2)	*Dipolotaxis harra*	The isolated compounds fit into the binding pocket of GSK3β and inhibited it in a PKC-dependent manner. It also showed PAR2-stimulated Caco-2 cell suppression by 20%.	[32]
Isoorientin (3)	*Eremurus spectabilis*	Isoorientin against HT29 cells decreased the CCND1 and CDK6 expression with significantly increased expressions of p21 and p53. Cell cycle arrest occurred at the G1/S checkpoint as a result of the reduced CCND1. Caspases 3 and 8 were activated as a result of the antiapoptotic protein Bcl-2 being suppressed, resulting in apoptosis. The ATR pathway was activated, resulting in lower levels of ATM, CHK1, and CHK2.	[34]

Furowanin A (4)	*Millettia pachycarpa*	Profilin 1 was identified as a target for furowanin A which induced apoptosis by cell cycle arrest. The isolated compound suppressed the colorectal cell growth and metastasis by the Pfn1 upregulation because Pfn1 with higher expression has been associated with colorectal cancer with long survival. Thus, by the upregulation of Pfn1, the metastasis of colorectal was achieved.	[35]
Pinocembrin (5)	*Elytranthe parasitica*	It promoted cell cycle arrest in G0/G1 phase, resulting in apoptosis and improved cytotoxicity.	[36]
3-hydroxy flavone (6)	*Muntingia calabyra*	The ROS accumulation lowered GSH levels on the DMH treatment which activated the NFκB transcription factor. Apoptosis was caused by the activation of caspase 3 and 9, the downregulation of connexin-43, and the p53 protein.	[37]
Indigocarpan (7)	*Indigofera aspalathoides*	It had stronger antiproliferative efficacy against colorectal cell lines and produced apoptosis in a dosage and time-dependent manner by halting the G2/M phase of the cell cycle. With the overexpression of p53 and p21, it increased caspase-3 cleavage, lowering the levels of cyclin D1 and B1.	[38]
Isoangustone A (8)	*Glycyrrhiza uralensis*	It induced autophagy by the significant inhibition of Akt/mTOR signaling, cellular ATP and mitochondrial respiration in a dose-dependent manner. It also activated AMPK with overexpression of AMPKα2 which significantly induced autophagy and cell death.	[39]
Periplocin (9)	*Telectadium dongnaiense*	The compound has improved antiproliferative properties and blocked the Wnt signaling pathway. Wnt target genes such as CMYC, CCND1, and BRIC5 reduced mRNA, C-myc, cyclin D1, and survival proteins levels. As a result, by blocking the Wnt/β-catenin signaling pathway, this downregulation decreased β-catenin signaling in a concentration-dependent manner and exerted improved activity.	[40]
Penduletin (10)	*Rhamnus disperma*	It induced apoptosis in a dose-dependent manner and arrested the cell cycle in the G1 phase.	[41]
Furowanin A (11)	*Millettia pachycarpa*	It enhanced autophagy and triggered apoptosis by suppressing cell proliferation by arresting cell cycles at the G1/G0 phase. By inhibiting the STAT3 signaling pathway and downregulating Mcl-1, apoptosis was induced via the STAT3/Mcl-1 axis.	[42]

ROS- Reactive oxygen species; GSK3β- Glycogen synthase kinase 3β; SIRT1- Sirtulin 1; AURKB- Aurokinase B; PARP- Polyadenosine diphosphate-ribose polymerase; p62/SQSTM1- Ubiquitin-binding protein p62; PKC- Protein kinase C; PAR2- Proteinase activated receptor 2; CCND1- Cyclin D1; CDK6- Cyclin dependent kinase 6; Atr- Serine-threonine protein kinase; ATM- Ataxia telangiectasia mutated gene; CHK- Checkpoint kinase; GSH- Glutathione; NF-κB- Nuclear factor-κB; CMYC- Myc proteo-oncogene protein; BRIC5- Baculoviral inhibitor of apoptosis repeat-containing 5; mTOR- Mammalian target of rapamycin; AMPK- AMP-activated protein kinase; AMPKα2- AMP-activated protein kinase α 2; STAT3- Signal transducer and activator of transcription 3; Mcl-1- Induced myeloid leukemia cell differentiation protein.

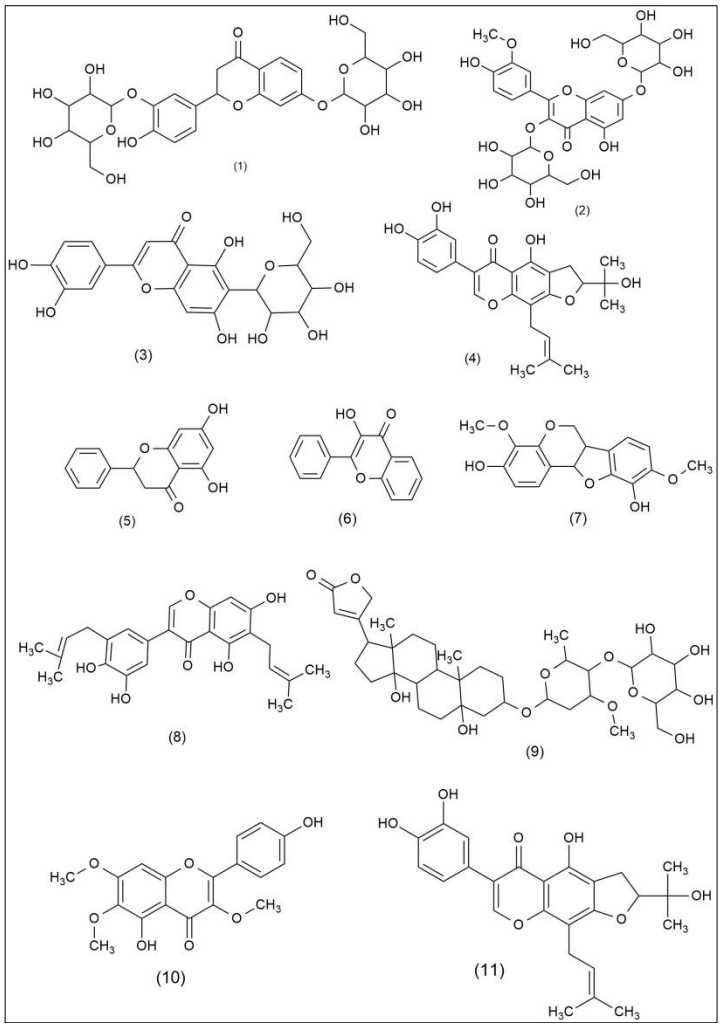

Fig 1: Structures of isolated flavonoids

2.2 Terpenoids

Terpenoids are another important phytoconstituent used in the treatment of colorectal cancer. The isolated phytoconstituents of terpenoids including nootkatone which was isolated from *Alpinia oxuphylla* displayed better anticolorectal activity via the induction of HO-1 and increased levels of expression of apoptotic proteins with significant suppression of cyclin D1 [43]. The triterpene Seco-acids decreased the cell viability via both dose and time-dependent manner. The triterpene Seco-acid against the DLD-1 colorectal cancer cell line exhibited increased apoptosis by the activation of caspase cleavage [44]. The daphnanes diterpene huratoxin from the latex of *Hura crepitans* against the Caco-2 cell line showed significant antiproliferative activity with 25.33 ± 9.71 % at 1µg/ml. This compound decreased the proliferative markers and induced the inhibition of GSK3β and Akt, which dysregulated the trafficking of β-catenin [45]. The various types of terpenoid compounds along with the sources, structures and mechanism is depicted in Table 2, Figure 2 and 3.

Table 2: Sources and mechanisms of isolated terpenoids

Phytochemicals (Compound number)	Source	Mechanism	Reference
Polyisoprenoids (Dolichol and polyprenol) (12)	*Nypa fruticans*	The expression of anti-apoptotic proteins Bcl-2 and cyclin D1 was reduced, and the cell cycle was arrested at the G0/G1 phase.	[1]
Sclareol (13)	*Sagittaria trifolia*	With cell cycle arresting in the G1 and G2/M phases, it had a stronger antiproliferative effect. In the mitochondrial route, ROS buildup occurred in a dose-dependent manner, inhibiting NFκB activation. The subsequential blockage of NFκB p65 phosphorylation was caused by the inhibition of IKKα/β and IKBα phosphorylation. In turn, the apoptotic factors like C-myc, cyclin D1 and Bcl-2 got downregulated.	[7]
Roburic acid (14)	*Arnebia euchroma*	It was found to be very effective against the HCT116 cancer cell line. It inhibited STAT1 activation and downregulated STAT3 activation expression.	[19]
Betulinic acid (15a) Betulonic acid (15b)	*Rhus chinensis*	Both of the isolated triterpenoids exerted better antiproliferative activity and induced apoptosis in a concentration-dependent manner. This compound also inhibited the levels of GLUT1, LDHA, PKM2, MCT1, NAD and NHE1 in dose-dependent manner. The inhibition of the ASIC2 upregulation leads to the downregulation of calcineurin and nuclear translocation of NFAT1 which influenced the calcineurin/NFAT1 pathway under acidosis. The targets were identified as ALDOA, PKM2 and LDHA.	[25]
Robustdial (16)	*Eucalyptus globulus*	The compounds are more antiproliferative and inhibited tyrosyl-DNA phosphodiesterase-2 (TDP-2).	[30]
Macrocarpal I (17)	*Eucalyptus globulus*	It substantially suppressed colorectal cell proliferation in a concentration-dependent manner. It induced apoptosis by inhibiting the phosphorylation of β-Raf, FEN1 gene which repairs DNA and downregulated the expression of FEN1.	[31]
Nootkatone (18)	*Alpinia oxyphylla*	It exhibited better activity and apoptosis effect by the suppression of cyclin D1 with a significant increase of NAG-I. The upregulation of NAG-I was due to EGR-1 which was increased by PPARγ transcriptional factor. Thus, the PPARγ binding activity was increased which increased the levels of EGR-1, leading to apoptosis.	[43]
Triterpo Seco-acid (3,4-Seco-olean-4(24)-en-19-oxo-3-oic acid) (19)	*Betula pubescens*	The externalization of phosphatidylserine triggered apoptosis. Apoptosis was caused by the activation of caspase 3, 7 cleavages and the destruction of PARP.	[44]
Huratoxin (20)	*Hura crepitans*	The antiproliferative and apoptotic activities were achieved by modulating the MAPK, GSK3β, Akt and YAP signals. Thus, the dysregulation of β-catenin trafficking occurred. The inhibition of these signals and the β-catenin pathway induced apoptosis.	[45]
β-Amyrin (21)	*Prunus Africana*	It showed significant cytotoxicity against the CaCo-2 cell line and the apoptotic effect was confirmed by the chromatin condensation, nuclear fragmentation, cell shrinkage and significant reduction of viable cells.	[46]
Aromadendrane-4β, 10β-diol (22)	*Curcuma kwangsiensis*	It blocked cancer cells from migrating in a time-dependent manner.	[47]
Cycloart-24-ene-26-ol-3-one (23)	*Aglaia exima*	Cytotoxicity was seen in both time and dose-dependent fashion. Caspase-8 activation was triggered by interaction with TNF-R1 and the activation of Bid protein. Through the mitochondrial pathway the activation of caspase 8 and 9 with the released cyt C and MMP production, the PARP cleavage and translocation of NFκB occurred, leading to apoptosis.	[48]
Clerodane (24)	*Tinospora cordifolia*	The release of Cyt C and MMP production activated caspase 9 via the mitochondrial route, promoting apoptosis. ROS production, Cyt C release, and nuclear translocation were all used to induce apoptosis.	[49]
Thymol (25)	*Thymus vulgaris*	Cell cycle arrest and inhibition of the Wnt/β-catenin signaling pathway by β-catenin inhibition were used to induce apoptosis. β-catenin, cyclin D1, C-myc, and survivin levels are all lowered as a result of the downregulation.	[50]
Limonoid (26)	*Swietnia macrophylla*	It showed promising activity and induced apoptosis by arresting the cell cycle at the G_2/M phase and significantly increased the expression levels of ATM, CHK2, Tp53, ARF, CDK1, CDKNIA and CASP3.	[51]
Loliolide and isololiolde (27)	*Heliotropium bacciferum*	The lactone terpenes were more effective at killing the HCT116 colorectal cancer cell line.	[52]

Bcl-2- B-Cell lymphoma 2; NF-β- Nuclear factor-β; IKKα/β- IκB kinase α/β; IκBα- Nuclear factor; STAT- Signal transducer and activator of transcription; GLUT1- Glucose transporter 1; LDHA- Lactate dehydrogenase; PKM2- Pyruvate kinase M2; MCT1- Monocarboxylate transporter 1; NAD- Nicotinamide adenine dinucleotide; NHE1- Sodium hydrogen exchanger 1; NFAT1- Nuclear factor of activated T cells-1; FEN1- Flap endonuclease 1; NAG-1- N-acetyl glucosamine-1; EGR-1- Earl growth response protein-1; PPARγ- Peroxisome proliferator-activated receptor-γ; PARP- Polyadenosine diphosphate-ribose polymerase; GSK3β- Glycogen synthase kinase 3β; MAPK- Mitogen activated

protein kinase; Akt- Serine-threonine protein kinase; YAP- Yes-associated protein kinase; MMP-Matrix metalloproteinase; ROS- Reactive oxygen species; ATM- Ataxia telangiectasia mutated gene; CHK2- Checkpoint kinase 2; ARF- Alternative reading frame; CDK-1- Cyclin dependent kinase 1; CDKNIA- Cyclin dependent kinase inhibitor A; CASP3- Caspase 3.

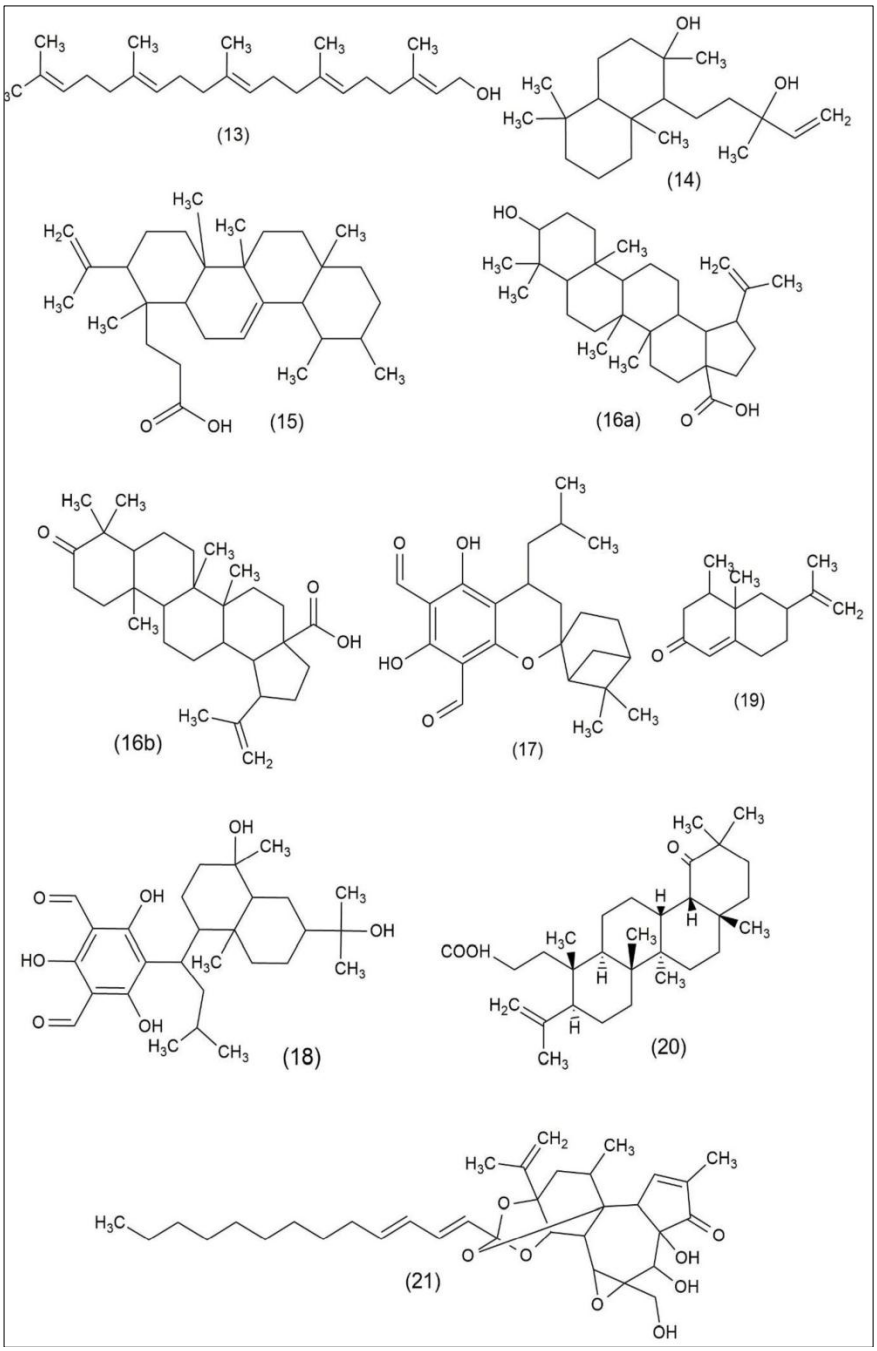

Fig 2: Structures of isolated terpenoids

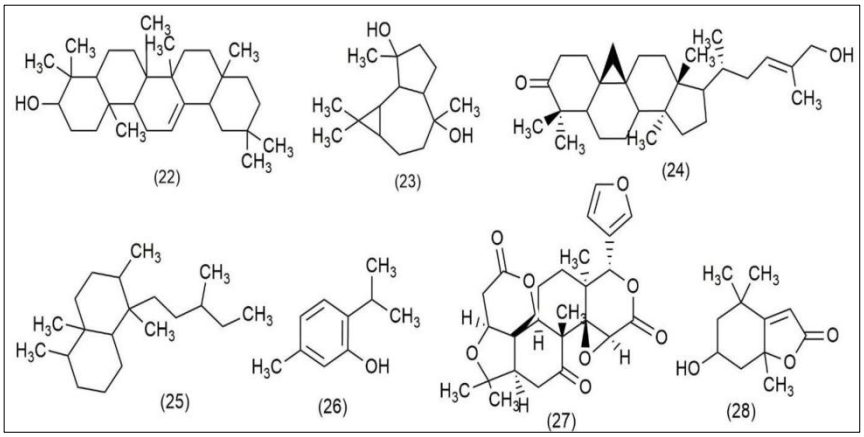

Fig 3: Structures of isolated terpenoids

2.2 Phenolics

Phenolic compounds also play an important role in the inhibition of tumor development and the formation of mutagenic compounds. Phenolic compounds with better anticancer efficacy also act as typical antioxidants. Compounds like pepper fruits are rich in antioxidants which also exhibited better cytotoxic activity. Phenolic substances, like other phytochemicals, cause apoptosis by blocking the NFκB signaling pathway. The isolated curcumin inhibited the STAT3 and NFκB signaling pathway by the activation of caspase 3 and 9 with the reduced CD24 level [16, 53].

While considering *Juglans regia*, the phenolic compound like catechin, chlorogenic acid, ellagic acid, gallic acid, etc., suppresse-d the growth of colon cancer cells. Along with the better anticancer efficacy, these compounds also had strong antioxidant compounds potential. The β-catenin/p-GSK3β signaling pathway was downregulated by these phenolic chemicals, which encouraged apoptosis. The phenolic extract of *Juglans regia* induced cell apoptosis by the downregulation of markers like CD133, CD44, DLK1 and Notch1. It contains enormous amounts of phenolic and polyphenolic compounds which are responsible for the better apoptosis potential [54]. The phenolic compounds like apiole derivatives of *Petroselinum crispum* promoted apoptosis in a dose-dependent manner with the induction of cell cycle arresting at G_0/G_1 phase. The tumor growth volume was determined using an *In vivo* nude mice model, which revealed that the isolated phenolic compound greatly decreased tumor development volume in athymic nude mice carrying COLO205 tumor cells. With the downregulation of cyclin D1, regulatory proteins and tumor suppressor proteins were increased while the cell cycle was arrested [55].

The compounds like hydroxycinnamic acid and hydroxybenzoic acids with anticancer activity also possessed antioxidant, anti-inflammatory and antimicrobial properties. The compounds or plants with high phenolic contents have a vital role in colorectal cancer. Thus, the purified phenolic extracts had better cytotoxicity against colorectal cancer cell lines than normal intestinal cells and also possessed 2-fold greater antioxidant activity than the crude extract. The extract from *Chaenomeles japonica* leaves indicated that the purified extract had better antioxidant and chemopreventive activities than the crude extract. It suggested that the purified form of the extract can be used as the natural source of chemopreventive agents in the future [14, 56]. The various phenolic and polyphenolic compounds like resveratrol, cannabidiol, coumaric acid, capsianosides, etc. along with their sources, structures and the apoptotic mechanism are given in Table 3 and Figure 4.

Table 3: Sources and mechanisms of isolated phenolics

Phytochemicals (Compound number)	Source	Mechanism	Reference
Capsianosides (28)	*Capsicum annuum*	It had a high level of cytotoxicity when tested against the HCT116 cancer cell line. No apoptosis mechanism was depicted.	[16]
Oblongifolin C and guttiferone K (29a and b)	*Garcinia yunnanensis*	Combined treatment of oblongifolin C and guttiferone K showed potent and synergistic activity and promoted apoptosis by increasing the PARP cleavage, activation and by arresting cell cycle at the G_1 phase.	[17]
Isoliquirtigenin (30)	*Glycyrrhiza uralensis*	Increased the percentage of apoptosis by inducing PARP cleavage and by increasing the caspase activation. The time-dependent upregulation of p62/SQSTM1 activated the caspase-8 dependent cell death.	[23]
Curcumin (31)	*Curcuma longa*	Apoptosis was achieved by the inhibition of STAT3 and NFκB signaling pathways mediated by the activation of caspase 3 and 9, followed by the downregulation of Sp1 and FAK.	[53]
(+)- catechin (32)	*Juglans regia*	The β-catenin/p-GSK3β signaling pathway was inhibited by the downregulation of tumor biomarkers like CD133, CD44, DCK1 and Notch1 in a dose-dependent manner.	[54]
Apiole (33)	*Petroselinum crispum*	It had higher cytotoxicity against the COLO205 cancer cell line and dose-dependently stopped the G0/G1 cell cycle. With the downregulation of cyclin D1, apoptosis-regulating and tumor-suppressing proteins were increased.	[55]
Cannabidiol (34)	*Cannabis sativa*	It induced apoptosis in a dose-dependent manner. The activation of Noxa enhanced the cleavage of PARP and caspases, resulting in apoptosis. The dose-dependent Noxa activation reduced MMP and ROS got accumulated in a short time. It induced apoptosis through the p53 independent pathway.	[57]
Resveratrol (35)	*Vitis vinifera*	Through the intrinsic route, it blocked the Wnt/β-catenin signaling pathway and triggered apoptosis. It suppressed the proliferation and nuclear condensation of β-catenin along with the downregulation of C-myc and cyclin D1. PARP cleavage boosted p53 protein levels, resulting in mitochondrial-mediated apoptosis.	[58]
Verbascoside (36)	*Osmanthus fragrans*	The suppression of IL-8, which blocked the NFκB nuclear translocation pathway, showed the most potent activity.	[59]
Ginnalin A (37)	*Acer tartaricum subsp. ginnala*	With a higher cell cycle arrest in the S phase, a better antiproliferative impact was seen. Stimulating Nrf2 translocation promoted apoptosis. The levels of Nrf2, NQO1, and HO-1 were downregulated as the amounts of mRNA increased. The Nrf2/HO-1 signaling pathway was thus activated, resulting in apoptosis.	[60]
Trans-p-coumaric acid (38)	*Imperata cylindrica*	It induced apoptosis through the ROS-Mitochondrial pathway. The ROS got accumulated and the apoptotic factors got increased, leading to apoptosis.	[61]
Vanillin (39)	*Echinochloa frumentacea*	In a concentration-dependent manner, significant cytotoxicity and apoptosis were accomplished, followed by cell cycle arrest at the G2 phase.	[62]
Trachelogenin (40)	*Combretum fruticosum*	Apoptosis was produced in both concentration and time-dependent manner. It promoted autophagy, which was followed by enhanced LC3 activation and a change in Bectin-1 expression, resulting in autophagosome formation and cytoplasmic vacuolization.	[63]

PARP- Poluadenosine diphosphate-ribose polymerase; STAT3- Signal transducer and activator of transcription 3; NFκB- Nuclear factor- κB; FAK- Focal adhesion kinase; CD133- Prominin 1 (Tumor marker); CD44- Homing cell adhesion molecule (Tumor marker); DCK-1- Dyskerin pseudouridine synthase 1; MMP- Matrix metalloproteinase; ROS- Reactive oxygen species; IL-8- Interleukin-8; Nrf-2- Nuclear factor erythroid-2; NQO1- NADPH Quinone dehydrogenase- 1; HO-1- Heme oxygenase-1; LC3- Microtubule-associated protein 1A/B-light chain 3.

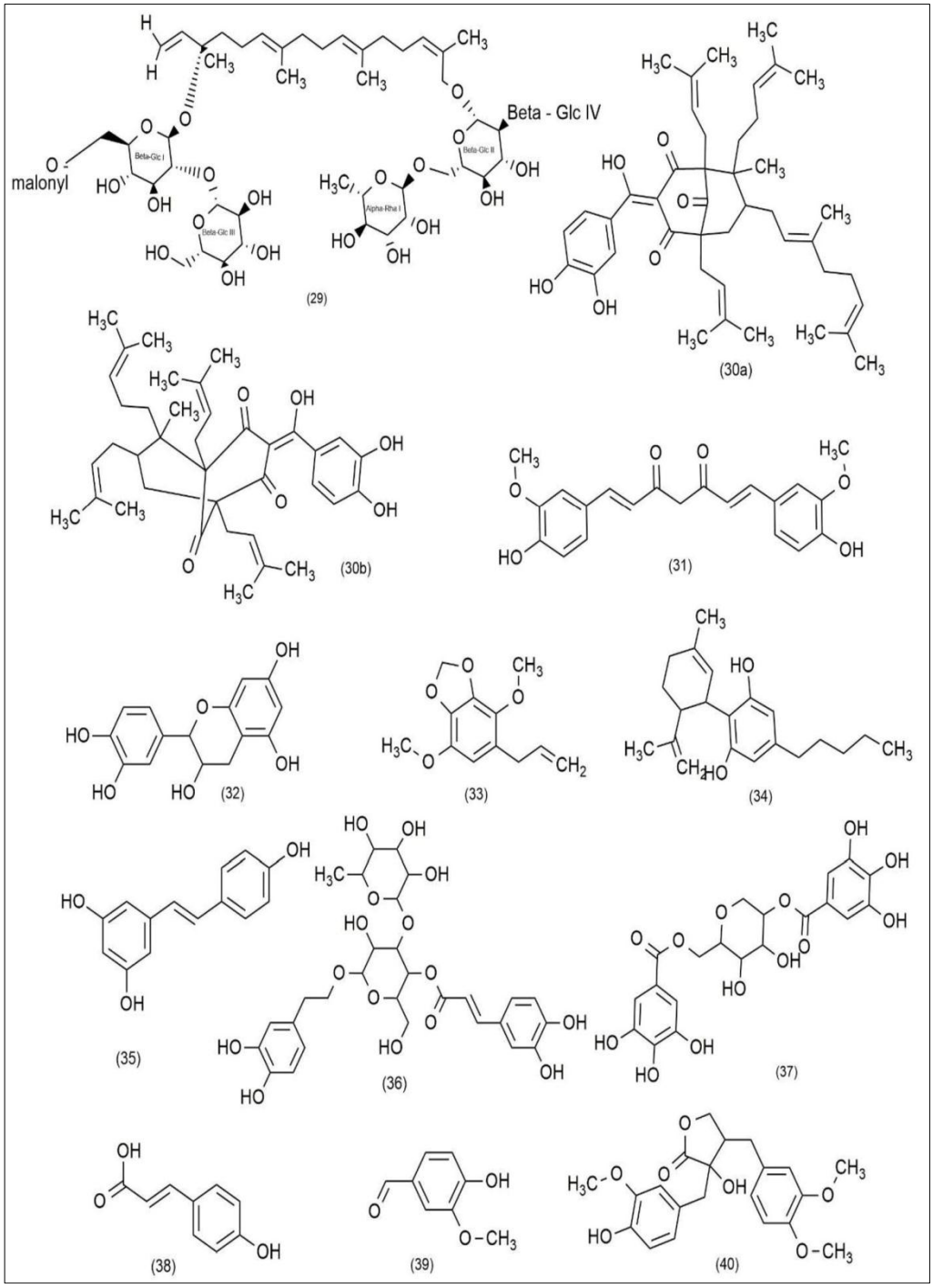

Fig 4: Structures of isolated phenolics

2.3 Alkaloids

The alkaloidal phytoconstituents also possessed better cytotoxic activity by inducing apoptosis through the various signaling pathways with the upregulation of several apoptotic proteins and tumor biomarkers. Pyrrolizidine alkaloids, such as nervosine VII, isolated from *Liparis nervosa*, promoted autophagy by activating caspase 3, 7, and 9 and upregulating LC3-II and bectin1 proteins while downregulating the p62 protein through the mitochondrial intrinsic route. It also caused apoptosis by activating the MAPK signaling pathway and inhibiting the p53 signaling pathway. The bisindole alkaloid like 3'R-hydroxytabernaelegantine isolated from *Tabernae montona* species against HCT116 and SW620 cell line possessed strong apoptosis induction than 5-fluorouracil. It caused apoptosis by activating caspases and inhibiting the anti-apoptotic protein Bcl-2 [22, 64].

GB7 acetate, a galbulimina alkaloid isolated from *Galbulimina belgraveana* against HCT116 upregulated the LC3 and p-AMPKα expression and induced autophagy. The autophagic cell death was further achieved by the downregulation of MMP2 and MMP9 production with simultaneous upregulation of E-cadherin occurred [65]. The various alkaloids like isoquinoline alkaloid [66], iboga alkaloid [67], pyranocarbazole alkaloids [68] possessed the cytotoxic potential and induced apoptosis with different mechanisms. The isolated alkaloids, their sources, structures along their mechanisms are depicted in Table 4 and Figure 5.

Table 4: Sources and mechanisms of isolated alkaloids

Phytochemicals (Compound number)	Source	Mechanism	Reference
Nervosine VII (41)	*Liparis nervosa*	The release of Cyt-C from mitochondria triggered apoptosis via modifying the intrinsic route, which activated caspase 3, 7, and 9. LC3-II and Bectin-1 protein levels were also upregulated, while p62 protein levels were downregulated. By the LC3-II upregulation, PARP cleavage was upregulated and the ERK1/2, JNK and p38 phosphorylation was also upregulated in a dose-dependent manner.	[22]
(3'R)-Hydroxy tabernaelegantine C (42)	*Tabernaemon tana elegans*	It triggered apoptosis by releasing Cyt C through the mitochondrial intrinsic route, which activated caspase 3 and 7.	[64]
GB7 acetate (43)	*Galbulimima belgraveana*	The autophagy was induced by the increased LC3-II expression and bectin-1 expression in a concentration-dependent manner and also significantly increased p-AMPKα. Moreover, apoptosis was induced by the suppression of MMP2/MMP9 expression levels in the HCT116 cells.	[65]
Protopine (44)	*Nandina domestica*	It induced apoptosis through the p53 activation pathway. With the activation of caspase 3 and 7, it increased the expression of $p21^{WAF1/CP1}$ and BAX.	[66]
Vobasinyl (45)	*Tabernaemon tana elegans*	The activation of caspase 3/7 caused apoptosis when the cell cycle was halted at the G2/M phase.	[67]
Murrayazoline (46)	*Murraya koenigii*	It induced apoptosis by the G_2/M phase cell cycle arresting. Through the mitochondrial pathway, the ROS accumulation got increased in a dose-dependent manner which induced the mitochondrial depolarization with the upregulation of Bax and downregulation of Bcl-2 protein. It also induced apoptosis through the Akt/mTOR survival pathway in which the Akt/mTOR phosphorylation got significantly reduced.	[68]
8-Acetonyl Dihydronitidine (47)	*Toddalia asiatica*	The apoptosis was induced by arresting the G_2/M phase cell cycle through p53 activation via a mitochondrial pathway with the upregulation of caspase 3 activations.	[69]
Scoulerine (48)	*Corydalis plants Corydalis cava*	In a dose-dependent manner, the compound reduced cell viability. With enhanced caspase-3/7 activation, Bax, and Cyt C expression, it triggered apoptosis via the intrinsic route. Downregulation of Bcl-2 resulted in the release of mitochondrial Cyt C. The ROS accumulation got increased and the apoptosis was further induced by ROS-dependent ER stress in HT29 and SW480 cells.	[70]

LC3- Microtubule-associated protein 1A/B-light chain 3; ERK1/2- Extracellular signal regulated kinase ½; JNK- c-JUN N- terminal kinase; AMPKα- AMP- activated protein kinase α; MMP- Matrix metalloproteinase; WAF-1- $p21^{WAF-1}$- Cyclin dependent kinase inhibition; CP1- Cystiene proteinase 1; Akt- Serine-threonine protein kinase; mTOR- Mammalian target of rapamycin; PARP- Polyadenosine diphosphate-ribose polymerase; Bcl-2- B-Cell lymphoma 2; ROS- Reactive oxygen species; ER- Endoplasmic reticulum.

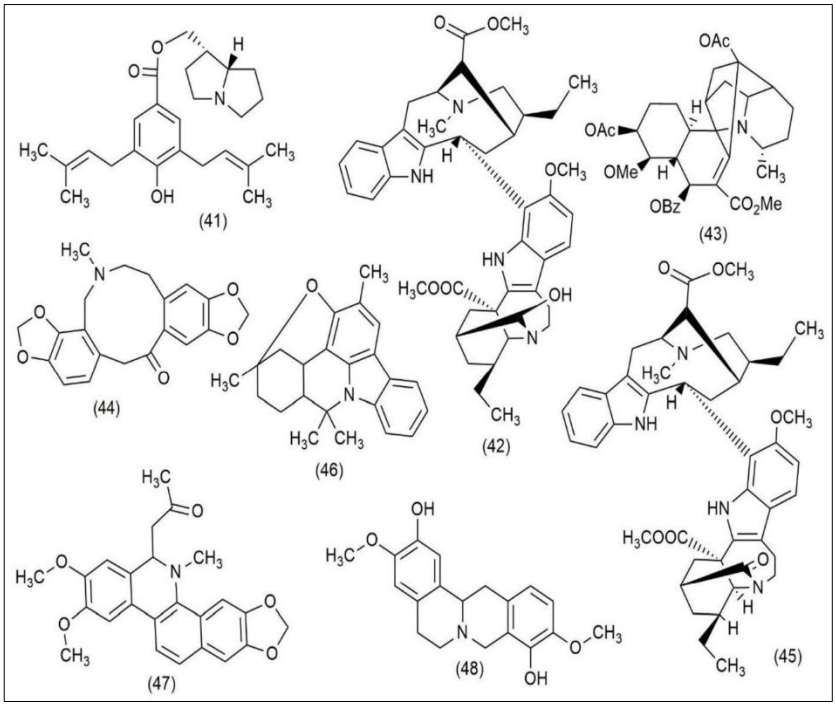

Fig 5: Structures of isolated alkaloids

2.4 Quinones

Naphthoquinones, which can be ortho or para naphthoquinones, are one of the most extensively distributed phenolics in plants. The compound β,β-dimethyl acrylshikonin was isolated from *Arnebia euchroma* which induced apoptosis by the inhibition of the STAT3 signaling pathway in HCT116 and SW620 colorectal cancer cells. The suppression of STAT3 resulted in a decrease in protein phosphorylation levels. A similar compound, Shikonin isolated from *Lithospermum erythrorhizon* inhibited cell survival through the inhibition of the SIRT2 signaling pathway. Thus, the alkaloids possessed different signaling pathways with better anticancer potential [19, 26].

The quinones exhibited better cytotoxic potential along with wide biological activities such as antimicrobial, antiparasitic and acetylcholine esterase inhibitors. The ortho naphthoquinone mansonone G and mansonone N obtained from *Mansonia gagei* exhibited strong cytotoxic efficacy against HCT116 colorectal cancer cells. The expression of P-glycoprotein, which is intended to increase ATPase activity, was suppressed by these isolated phytochemicals [71]. Like naphthoquinones, the anthraquinones, benzoquinones and polyquinones having di-one and di-ketone systems also played a major role in colorectal carcinogenesis with enormous biological applications. The compound plumbagin which is naphthoquinone and rapanone, a benzoquinone isolated from the Kenyan flora exhibited better anticancer activity against DLD-1 cells. These isolated compounds caused apoptosis via the intrinsic route, which involved the buildup of reactive oxygen species (ROS) and the downregulation of MMP [72]. The sources, structures and mechanism of the isolated quinones are given in Table 5 and Figure 6.

Table 5: Sources and mechanism of isolated quinones, xanthones and coumarins

Phytochemicals (Compound number)	Source	Mechanism	Reference
Quinones			
β,β-dimethyl aryl shikonin (49)	*Arnebia euchroma*	It induced apoptosis by the inhibition of the STAT3 signaling pathway in HCT116 and SW620 colorectal cancer cells. The suppression of STAT3 resulted in a decrease in protein phosphorylation levels.	[19]
Shikonin (50)	*Lithospermum erythrorhizon*	It inhibited cell survival through the inhibition of the SIRT2 signaling pathway and similar to the previous compound.	[26]
Mansonone G (51a) and Mansonone N (51b)	*Mansonia gagei*	It exhibited strong cytotoxic efficacy against HCT116 colorectal cancer cells. The expression of P-glycoprotein, which is intended to increase ATPase activity, was suppressed by these isolated phytochemicals.	[71]
Plumbagin (52) and rapanone (53)	*Kenyan flora*	These isolated compounds caused apoptosis via the intrinsic route, which involved the buildup of reactive oxygen species (ROS) and the downregulation of MMP.	[72]
Xanthones			
Garcinone E (61), Mangostanaxantone IV (62), α-mangostin (63)	*Garcinia mangostona*	It exhibited potent activity with IC_{50} values ranging from 15.8 to 16.7 µM. The compound garcinone E arrested the G_0/G_1 phase cell cycle with induced necrosis. Against HCT116 colorectal cancer cells, the compound mangostanaxanthone induced apoptosis and necrosis, whereas α- mangostin only promoted moderate necrosis.	[8]
(-)-gambogic acid (64)	*Garcinia hanburyi*	Best known caged xanthone – Mechanism was not depicted.	[80]
Neobractatin (65a), Methylbractatin (65b), Bractatin (65c)	*Garcinia propinqia*	It showed a substantial cytotoxic action, with IC_{50} values of 2.60, 7.02, 1.47, 3.37, and 4.14 µM, respectively	[80]
Ditunggarcinone J (66a) and Ditunggarcinone K (66b)	*Garcinia propinqia*	The significant cytotoxicity was achieved against HCT116 cancer cells with IC_{50} values of 14.23 and 23.95 µM, respectively	[81]
Euxanthone (67)	*Polygala caudata*	It induced apoptosis through targeting the CIP2A/PP2A pathway in which the blockade of CIP2A overexpression has occurred. The apoptosis of colorectal cancer cells was affected by CIP2A knockdown followed by sensitization.	[82]
Coumarins			
Mansonin a-c (68a-c) and mansonin I-III (69a-c)	*Mansonia gagei*	These compounds hindered the P-glycoprotein pump by inhibiting ATPase subunits and occupying binding sites. Mansorin II was found to have a synergistic effect with paclitaxel, causing cell cycle arrest in the G2/M phase.	[71]
8-methoxypsoralen (70)	*Ammi majus*	This compound against SW620 cancer cells exhibited better activity with the reduced AKT^{308} phosphorylation. Bcl-2, an anti-apoptotic protein, was downregulated, whereas Bax and caspase activation were upregulated. As a result, both intrinsic and extrinsic mechanisms were used to trigger apoptosis. i.e., PI3K/Akt signaling pathway.	[85]

STAT3- Signal transducer and activator of transcription-3; SIRT2- Sirtulin 2; ROS- Reactive oxygen species; MMP- Matrix metalloproteinase; CIP2A/PP2A- Cyclin-dependent kinase inhibitor/Protein phosphatase 2A; Bcl-2- B-Cell lymphoma-2; AKT- Serine-threonine protein kinase.

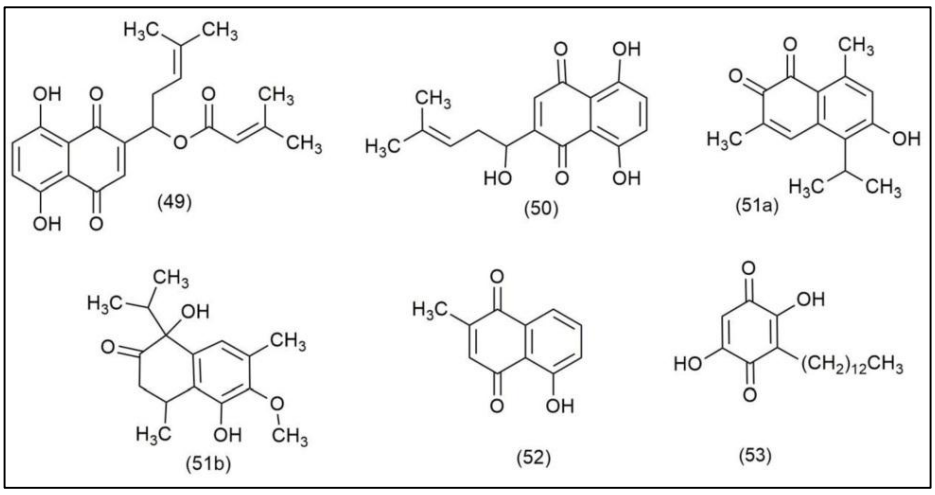

Fig 6: Structures of isolated quinones

2.5 Saponins

The saponins influenced carcinogenesis through various signaling pathways. Saponins are widely dispersed and abundant in the average person's diet. Carcinogenesis, as well as other biological activities such as chronic disorders like diabetes, cardiology, and neurological diseases, were linked to saponin intake. The isolated saponin, jujuboside B from *Zizyphus jujuba* induced apoptosis through an intrinsic pathway with the downregulation of the PI3K/Akt pathway. It also promoted ROS generation along with the simultaneous inhibition of PI3K/Akt signaling [73]. The saponins also induced apoptosis through other signaling pathways like the NF-κB signaling pathway [74], MAPK signaling pathway [75], BAX/BCL-2 pathway [76], etc. The compound PP9 (Pennogenin-3-O-α-L-rhamnopyranosyl-(1→4)-[α-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside), which is a steroidal saponin obtained from the rhizomes of *Paris polyphylla* influenced apoptosis through PI3K/Akt/GSK3β pathway. With both time and dose-dependent decrease of cell viability, this compound triggered G2/M phase cell cycle arrest. Upregulation of p21 and downregulation of CDC25C, cyclin B1, and CDC2 were used to produce cell cycle arrest. The suppression of PI3K/Akt/GSK3β signaling was achieved by the activation of PARP, caspase 3 and 9 cleavages with simultaneous downregulation of anti-apoptotic protein Bcl-2 [77]. The various saponins along with their source, structures and mechanisms are given in Table 6 and Figure 7.

Table 7: Sources and mechanisms of isolated saponins

Phytochemicals (Compound number)	Source	Mechanism	Reference
Diosgenin (54)	*Dioscorea alata*	Both time and dose-dependent activation of the cytotoxic potential were observed. Increased generation of ROS and reduced MMP triggered apoptosis via the intrinsic route. It also suppressed the Bcl-2 expression with significant upregulation of Bax, p53, caspase 3 and PARP.	[27]
Jujuboside B (55)	*Zizyphys jujuba*	The apoptosis was promoted through the mitochondrial pathway. It caused apoptosis by increasing ROS production and inhibiting the PI3K/Akt signaling pathway. The caspase-3 got activated by the release of Cyt C and promoted PARP cleavage.	[73]
Esculentoside H (56)	*Phytolacca esculenta*	The downregulation of MMP9 expression reduced PMA-induced cell migration in a dose-dependent manner. The nuclear factor-κB signaling was associated with MMP9, thus, the NF-κB signaling translocation was suppressed. Finally, the inhibition of NF-κB signaling mediated MMP9 expression suppressed the cell migration.	[74]
Ginsenoside (57)	*Panax japonicus*	Upregulation of Bax, Bad, and caspase cleavage, as well as downregulation of anti-apoptotic proteins Bcl-2, Bcl-x, and Mcl-1, resulted in the arrest of the S and G0/G1 phase cell cycles and the induction of apoptosis. It also blocked the p38 mitogen-activated protein kinase (MAPK) signaling pathway, which caused apoptotic proteins to be triggered.	[75]
Rinoxia B (58)	*Datura inoxia*	It caused cell cycle arrest in the S and G2/M phases, as well as apoptosis through the intrinsic pathway. Upregulation of Bcl-2 accompanied by downregulation of anti-apoptotic proteins, tumor suppressors p53 and p21, and cell cycle regulators cyclin B1 and D1 increased Cyt C release and caspase activation.	[76]
PP9 (Pennogenin-3-O-α-L-rhamnopyranosyl-(1→4)-[α-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside) (59)	*Paris polyphylla*	Upregulation of tumor suppressor p21 and downregulation of cell cycle regulators cyclin B1, CDC25C, and CDC2 resulted in cell cycle arrest at the G2/M phase. Through the PI3K/Akt/GSK3β signaling pathway, the anti-apoptotic proteins got suppressed and promoted the PARP cleavage and caspase activation.	[77]
Aglycone oleandrigenin (2'-O-actylacoschimproside (), Oleandrigen-3-O-α-L-2'-O-acetylvallaropyranoside) (60b)	*Vallaris glabra*	With IC_{50} values ranging from 0.03-0.07 µM, it showed significant cytotoxic action against the HTB38 cell line.	[78]
Crude saponins from fruits	*Zanthoxylum armatum*	The development of apoptotic bodies triggered apoptosis. Chromatin condensation and nuclear fragmentation.	[79]

ROS- Reactive oxygen species; MMP- Matrix metalloproteinase; PARP- Polyadenosine diphosphate-ribose polymerase; Bcl- B-Cell lympoma; PI3K- Phosphoionisitide 3 kinase; Akt- Serine-threonine protein kinase; GSK3β- Glycogen synthase kinase 3β; PMA- Phorbol 12-myristate 13-acetate; NF-κB- Nuclear factor- κB; MAPK- Mitogen activated protein kinase; CDC25C and CDC2- Cyclins of specific phosphatase family.

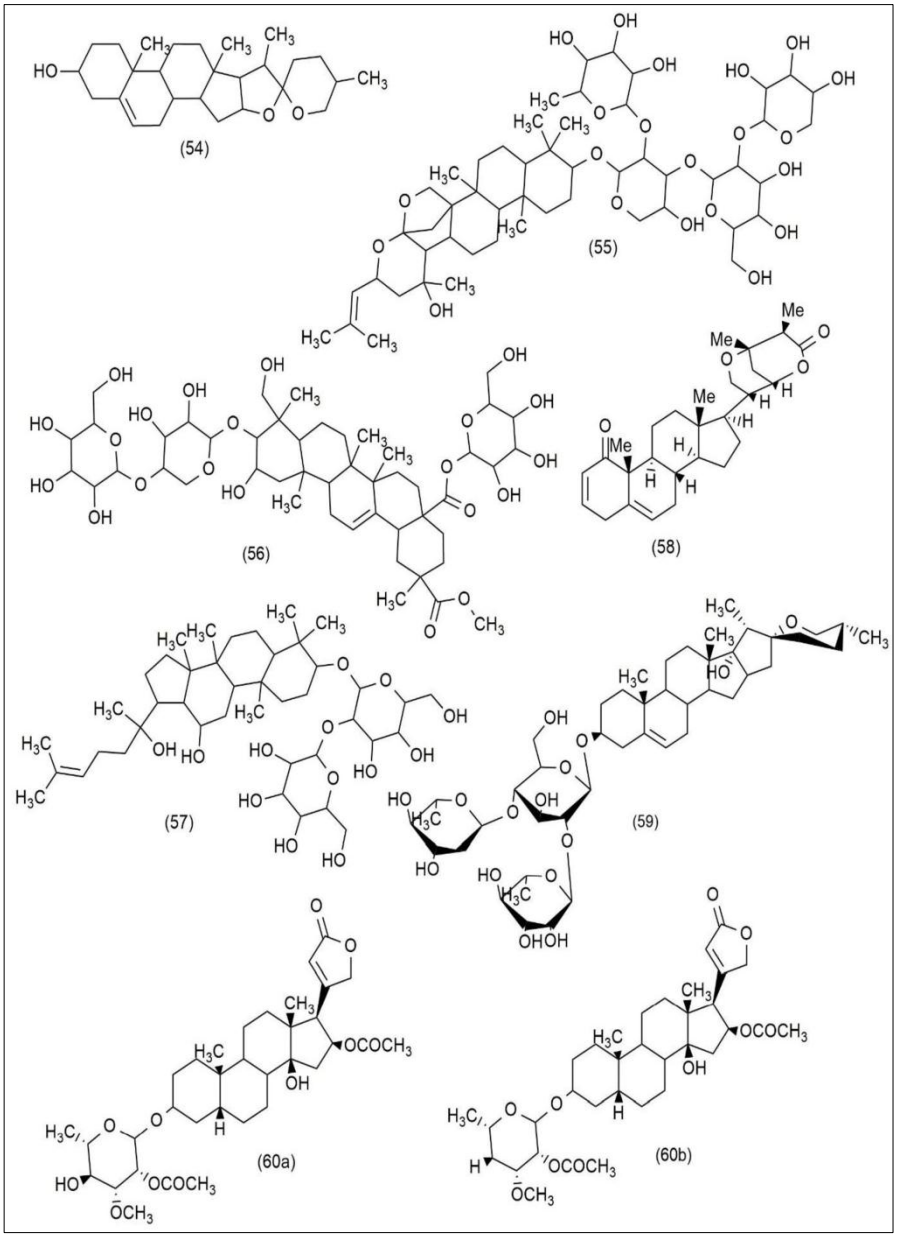

Fig 7: Structures of isolated saponins

2.6 Xanthones

Cell cycle arrest and apoptosis were also triggered by xanthones in colorectal cancer cell lines. The mangastanaxanthones like garcinone E, mangostanaxanthone IV and α- mangostin isolated from *Garcinia mangostona* exhibited potent activity with IC_{50} values ranging from 15.8 to 16.7 µM. The compound garcinone E arrested the G_0/G_1 phase cell cycle with induced necrosis. Against HCT116 colorectal cancer cells, the compound mangostanaxanthone induced apoptosis and necrosis, whereas α- mangostin only promoted moderate necrosis [8].

The caged xanthones showed wide biological activities particularly having a greater potential towards carcinogenesis. The best known caged xanthones were (-)- gambogic acid which was isolated from the secreted resin of *Garcinia hanburyi*. The caged xanthones (+)- neobractatin, (-)- neobractatin, (+)- 3-O-methylbractatin, (-)- 3-O-methylbractatin, and (-)- bractatin showed a substantial cytotoxic action, with IC_{50} values of 2.60, 7.02, 1.47, 3.37, and 4.14 µM, respectively, *Garcinia propinqua* yielded scalemic caged xanthones that were similar. The caged xanthones ditunggarcinone J and K, with IC_{50} values of 14.23 and 23.95 µM respectively, showed significant cytotoxicity against HCT116 cancer cell lines [80,81]. Then, the flavonoid xanthone, euxantone isolated from *Polygala caudata* induced apoptosis through targeting the CIP2A/PP2A (Cyclin-dependent kinase inhibitor/Protein phosphatase 2A) pathway in which the blockade of CIP2A overexpression has occurred. The apoptosis of colorectal cancer cells was affected by CIP2A knockdown followed by sensitization [82]. The source, structures and mechanism of the isolated xanthones are given in Table 5 and Figure 8.

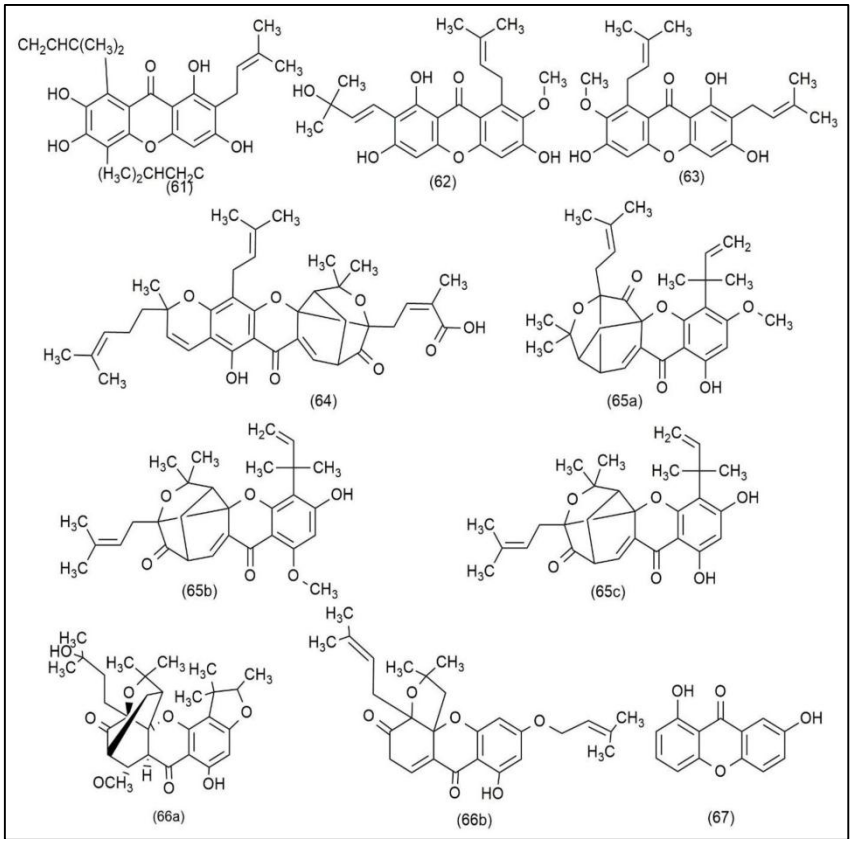

Fig 8: Structures of isolated xanthones

2.7 Iridoids

Iridoids, the valepotriates with greater interest in nature have wide biological significance over cancer and other diseases. It was derived from *Valerina jatamansi*, which caused HCT116 and HCT8 colorectal cancer cells to die. The chlorovaltrate compounds of valepotriates had the cytotoxic potential and the compound valral C induced apoptosis through the PDK1/Akt/mTOR pathway via the suppression of Akt/mTOR. The valepotriate isomers, specifically jatamanvaltrates, had a mild effect on HCT8 cells. As a result, the chlorovaltrates outperformed the jatamanvaltrates in terms of cytotoxicity against colorectal cancer cells [83, 84].

2.8 Coumarins

Coumarins are also one of the potent anticancer agents that occurred naturally. It's benzopyrones, which are naturally occurring and have a variety of biological applications. Coumarins primarily exert their cytotoxic potential via inhibiting the telomerase enzyme, protein kinase inhibition, and oncogene downregulation. It also triggers apoptosis via an intrinsic signaling route and other signaling pathways. The coumarins isolated from *Mansonia gagei* include mansorin A, B, C and mansorins I, II, III. These drugs hindered the P-glycoprotein pump by inhibiting ATPase subunits and occupying binding sites. Mansorin II was found to have a synergistic effect with paclitaxel, causing cell cycle arrest in the G2/M phase. The classical photochemotherapeutic agent 8-methoxypsoralen, a furanocoumarin obtained from *Ammi majus*. This compound against SW620 cancer cells exhibited better activity with the reduced AKT^{308} phosphorylation. Bcl-2, an anti-apoptotic protein, was downregulated, whereas Bax and caspase activation were upregulated. As a result, both intrinsic and extrinsic mechanisms were used to trigger apoptosis. i.e., PI3K/Akt signaling pathway [71,85]. The source, structures and mechanism of the isolated coumarins are given in Table 5 and Figure 9.

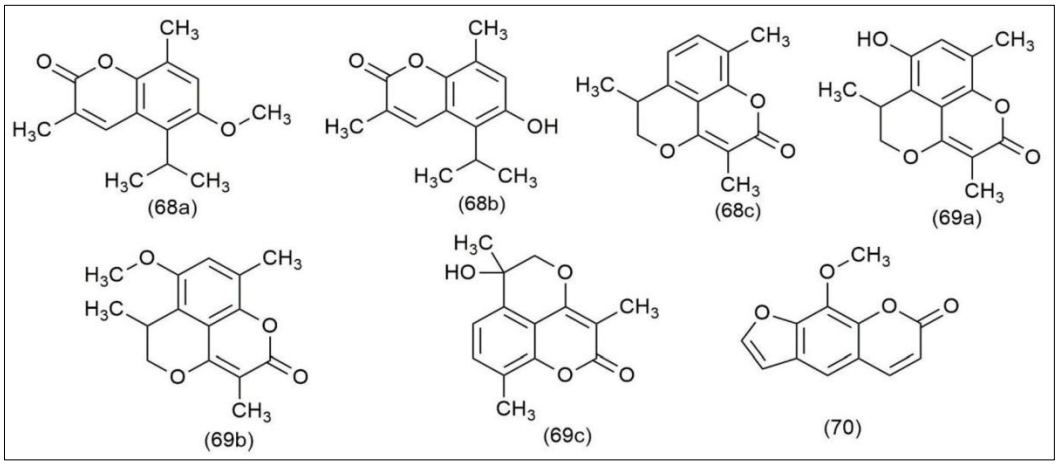

Fig 9: Structures of isolated coumarins

2.9 Miscellaneous Compounds

The secondary metabolites like essential oils extracted from aromatic plants are comprised of multifunctional chemical compounds which are responsible for the therapeutic activity. The amount and concentration of oxygenated molecules and hydrocarbons in essential oils determine their biological action. The isoledene rich oleo-gum resin containing essential oils from *Mesua ferrea* induced apoptosis through the downregulation of surviving, HSPs and xIAP with the upregulation of ROS expression, caspase activation in the HCT116 colorectal cancer cell line [12, 86].

In colorectal cancer, withanolides, a category of steroidal lactones, has a function in cell cycle arrest and death. At low doses, the 4-hydroxywithanolide E derived from *Physalis peruviana* activated the G0/G1 phase cell cycle and promoted apoptosis via inhibiting c-Jun activity with SIRT1 increase and down regulated the Hsp90 protein and PTGS2 [87]. The other secondary metabolite, pectin extracted from *Carica papaya*, blocked galectin-3, hence inhibiting the proliferation of colorectal cancer cells. Pectin is a polysaccharide that helps plants maintains their integrity and immunity. To inhibit carcinogenesis, pectin components interact with the carbohydrate recognition domain of the prometastatic protein galectin [88].

Foveoglin A from *Acrosticta foveolate* leaves, perviridisin B from *Aglaia perviridis*, and aglaodoratin D from *Aglaia odorata* displayed stronger and more powerful cytotoxicity against several cancer cell lines. The aglotorbesin derivative triggered apoptosis by activating caspases and fragmenting DNA [89]. The compounds of essential oils, triglycerides, oleo-gum resins, pectin, withanolide and aglotorbesin derivative along with their sources, structures and mechanism are depicted in Table 7 and Figure 10.

Table 7: Sources and mechanisms of miscellaneous phytochemicals

Phytochemicals (Compound number)	Source	Mechanism	Reference
Riccardin D (71)	*Dumortiera hirsuta*	The isolated compound decreased the growth of HT29 cells considerably. By lowering NF-κB nuclear translocation, apoptosis was induced. With the downregulation of tumor necrosis factor-β (TNF-β), PARP and caspase cleavage were activated.	[20]
Pogostone (72)	*Pogestemon cablin*	The apoptosis through the Akt/mTOR signaling pathway, whereas the upregulation of LC3-II expression, caspase cleavage and downregulation of Akt/mTOR phosphorylation occurred.	[24]
Isoledene rich oleo gum (73)	*Mesua ferrea*	It downregulated the levels of survivin, HSPs with upregulation of ROS production and caspase-3/7 activation in HCT116 cells.	[86]
4β-hydroxywithanolide E (74)	*Physalis peruviana*	The increase of p21 hindered cell proliferation. The apoptosis was achieved by the c-Jun inhibition activity, whereas the SIRT1 got elevated. With the downregulation of PTGS2 and HSP90 expression, the G0/G1 phase cell cycle was halted.	[87]
Pectin (75)	*Carica papaya*	The galectin-3 overexpression was inhibited which induced apoptosis i.e., the pectin factor interacted with the carbohydrate recognition domain of the pro-metastatic protein, galectin.	[88]
Aglatorbesin derivative (76)	*Aglaia loheri*	Through the activation of caspase 3/7 and the enhancement of apoptotic signaling, it triggered apoptosis.	[89]
Isoledene (77)	*Mesua ferrea*	Apoptosis was achieved via the intrinsic pathway. The induction of pro-apoptotic proteins Bid, Bim, and Cyt C was associated with increased levels of ROS generation, caspase-3, 8, and 9, while anti-apoptotic proteins such Bcl-2, Bcl-w, survival, xIAP, and HSPs were downregulated. In HCT116 cells, cell cycle arrest at the G0/G1 phase was accomplished.	[90]
Tripolinolate (78)	*Tripollium vulgare*	By inhibiting the G2/M phase of the cell cycle, it caused apoptosis. On tumor-bearing mice, better anti-colorectal cancer efficacy was achieved.	[91]
Polygonumin A (79)	*Polygonum minus*	With an IC_{50} of 3.24 0.73 µg/ml, it showed superior cytotoxic action against the HCT116 cell line.	[92]
3,5-dihydroxy-2,4-dimethyl-1-O-(6'-O-galloyl-β-D-glucopyranosyl)-benzophenone (80)	*Psidium guajava*	The cell viability of HCT116 cancer cells was decreased in a dose-dependent manner. Further, the apoptotic signaling was achieved by the upregulation of p53, p-ERK1/2, p-JNK and caspase 8,9 cleavage. Thus, DNA damage occurred and apoptosis was achieved.	[93]
Tricaproin (81)	*Simarouba glauca*	With enhanced p21 expression, it caused cell cycle arrest in the G0/G1 phase. The tumor markers Ki67 and CD31 got downregulated, whereas the caspase-3 cleavage got increased.	[94]

NF-κB- Nuclear factor-κB; TNF-β- Tumor necrosis factor-β; PARP- Polyadenosine diphosphate-ribose polymerase; Akt- Serine-threonine protein kinase; mTOR- Mammalian target of rapamycin; LC3- Microtubule-associated protein 1A/B-light chain 3; ROS- Reactive oxygen species; SIRT1- Sirtulin 1; PTGS2- Prostaglandin endoperoxide synthase 2; HSP- Head shock protein; xIAP- x-linked inhibitor of apoptosis protein; Bcl- B-Cell lymphoma; ERK 1/2- Extracellular regulated protein kinase 1/2; JUK- c-JUN N-terminal kinase.

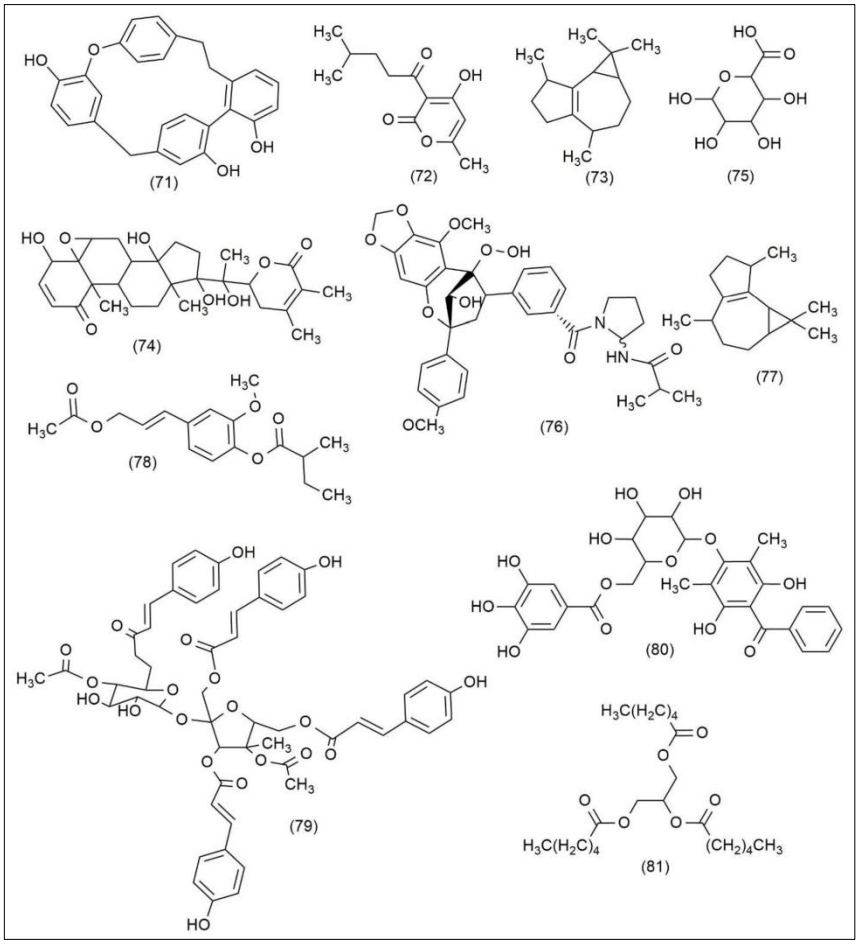

Fig 10: Structures of miscellaneous phytochemicals

3. Future directions and limitations

Chemotherapy and other medicines used in the past have the potential to destroy living cells. Thus, in the future, the plant materials or isolated phytoconstituents can be used to replace the conventional synthetic agents. The non-nutritive plant-based diet has the potential to be anticarcinogenic. While the plant sources and their constituents act as anticancer agents, most dietary constituents enhanced the risk of cancer with a negative correlation with nutrients. Several studies have also found a link between colorectal cancer risk and dietary elements.

4. Conclusion

The incidence of colorectal cancer is on the rise these days, indicating a need for better medication or treatment. Despite the fact that several conventional remedies have been described, they have a number of limitations. The use of chemotherapeutic agents has some drawbacks including toxicity, adverse effects on various organs, affecting the cell viability of normal cells and decrease in the life span of patients. Thus, the phytochemicals are used to replace the conventional synthetic drugs as a complementary therapy with less/no toxicity and ecofriendly. The various phytochemicals present in the plants include flavonoids, phenolics, polyphenolics, terpenoids, alkaloids, coumarins, steroidal saponins, xanthones, iridoids, quinones and other secondary metabolites used in the colorectal cancer treatment is emphasized. These phytochemical compounds exerted their activity against various anticolorectal cancer cell lines like HCT116, HCT115, HCT8, SW480, SW620, DLD-1, HT29, COLO205 and LOVO cells. They induced cell cycle arrest at various stages and used intrinsic and extrinsic signaling mechanisms to induce anticancer apoptosis. The phytochemicals demonstrated their effectiveness by inhibiting multiple signaling pathways. Thus, the phytochemicals can be used as a feasible method of treatment to overcome the drawbacks associated with other conventional therapies. There is also in need for further support to use plant phytoconstituents and their isolated compounds as marketed products in the future.

5. Acknowledgement

We thank the Management and Dr. G. Murugananthan, Principal of our college for giving constant support and encouragement for writing this review.

Source of Support and Funding: Nil

Authors Contribution

All the authors had contributed equally.

Conflicts of Interest: Nil

6. References

1. Sari D, Basyuni M, Hasibuan P, Sumardi S, Nuryawan A, Wati R. Cytotoxic and Antiproliferative Activity of Polyisoprenoids in Seventeen *Mangroves* Species Against WiDr Colon Cancer Cells. Asian Pac J Cancer Prev. 2018;19(12):3393-3400. doi: 10.31557/APJCP.2018.19.12.3393.
2. Sung H, Ferlay J, Rebeca L, Siegel MPH, Laversanne M, Soejomataram I, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality

Worldwide for 36 Cancers in 185 Countries. CA: Cancer J Clin. 2021;71(3):209-249. doi: 10.3322/caac.21660.
3. Subramaniyan B, Kumar V, Mathan G. Effect of sodium salt of Butrin, a novel compound isolated from *Butea monosperma* flowers on suppressing the expression of SIRT1 and Aurora B kinase-mediated apoptosis in colorectal cancer cells. Biomed Pharmacother 2017;90:402-413. doi: 10.1016/j.biopha.2017.03.086.
4. Harlid S, Gunter MJ, Guelpen VB. Risk-Predictive and Diagnostic Biomarkers for Colorectal Cancer; a Systematic Review of Studies Using Pre-Diagnostic Blood Samples Collected in Prospective Cohorts and Screening Settings. Cancers. 2021;13(17):4406. doi: 10.3390/cancers13174406.
5. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Walace MB. Colorectal cancer. Lancet. 2019;394(10207):1467-1480. doi: 10.1016/S0140-6736(19)32319-0.
6. Choi JW, Lee J, Kim SC, You S, Lee CW, Shin J, *et al*. Glucuronorhamnoxylan from *Capsosiphon fulvescens* inhibits the growth of HT-29 human colon cancer cells *In vitro* and *In vivo* via induction of apoptotic cell death. Int J Biol Macromol. 2019;124:1060-1068. doi: 10.1016/j.ijbiomac.2018.12.001.
7. Assani I, Du Y, Wang CG, Chen L, Hou PL, Zhao SF, *et al*. Anti-proliferative effects of diterpenoids from *Sagittaria trifolia* L. tubers on colon cancer cells by targeting the NF-κB pathway. Food Funct. 2020;11:7717-7726. doi: 10.1039/d0fo00228c.
8. Mohamed GA, Al-Abd AM, El-Halawany AM, Abdallah HM, Ibrahim SRM. New xanthones and cytotoxic constituents from *Garcinia mangostana* fruit hulls against human hepatocellular, breast, and colorectal cancer cell lines. J Ethnopharmacol. 2017;198:302-312. doi: 10.1016/j.jep.2017.01.030.
9. Khan GN, Kumar N, Ballal RA, Datta D, Belle VS. Unveiling antioxidant and anti-cancer potentials of characterized *Annona reticulata* leaf extract in 1,2-dimethylhydrazine-induced colorectal cancer in Wistar rats. J Ayurveda Integr Med. 2021;12(4):579-589. doi: 10.1016/j.jaim.2021.05.010.
10. Opattova A, Horak J, Vodenkova S, Kostovcikova K, Cumova A, Macinga P, *et al*. *Ganoderma Lucidum* induces oxidative DNA damage and enhances the effect of 5-Fluorouracil in colorectal cancer *In vitro* and *In vivo*. Mutat Res Genet Toxicol Environ Mutagen. 2019;845:403065. doi: 10.1016/j.mrgentox.2019.06.001.
11. Zubair MS, Anam S, Lallo S. Cytotoxic activity and phytochemical standardization of *Lunasia amara* Blanco wood extract. Asian Pac J Trop Biomed. 2016;6(11):962-966. doi: 10.1016/j.apjtb.2016.04.014.
12. Beeby E, Magalhaes M, Pocas J, Collins T, Lemos MFL, Barros L, etb al. Secondary metabolites (essential oils) from sand-dune plants induce cytotoxic effects in cancer cells. J Ethnopharmacol. 2020;258:112803. doi: 10.1016/j.jep.2020.112803.
13. Murayyan AI, Manohar CM, Hayward G, Neethirajan S. Antiproliferative activity of Ontario grown onions against colorectal adenocarcinoma cells. Food Res Int. 2017;96:12-18. doi: 10.1016/j.foodres.2017.03.017.
14. Chojnacka K, Sosnowska D, Polka D, Owczarek K, Gorlach-Lira K, Oliveira de Verasa B, *et al*. Comparison of phenolic compounds, antioxidant and cytotoxic activity of extracts prepared from *Japanese quince* (*Chaenomeles japonica* L.) leaves. J Physiol Pharmacol 2020, 71(2). doi: 10.26402/jpp.2020.2.05.
15. Chowdhury S, Poddar SK, Zaheen S, Noor FA, Ahmed N, Haque S, *et al*. Phytochemical screening and evaluation of cytotoxic and hypoglycemic properties of *Mangifera indica* peels. Asian Pac J Trop Biomed 2016;7(1):49-52. doi: 10.1016/j.apjtb.2016.09.009.
16. Chilczuk B, Marciniak B, Stochmal A, Pecio L, Kontek R, Jackowska I, *et al*. Anticancer Potential and Capsianosides Identification in Lipophilic Fraction of Sweet Pepper (*Capsicum annuum* L.). Molecules. 2020;25(13):3097. doi: 10.3390/molecules25133097.
17. Li H, Meng XX, Zhang L, Zhang BJ, Liu XY, Fu WW, *et al*. Oblongifolin C and guttiferone K extracted from *Garcinia yunnanensis* fruit synergistically induce apoptosis in human colorectal cancer cells *In vitro*. Acta Pharmacol Sin. 2017;38:252-263. doi: 10.1038/aps.2016.101.
18. Mahmoud IF, Kanthimathi MS, Aziz AA. ROS/RNS-mediated apoptosis in HT-29 colorectal cancer cells by methanolic extract of *Tamarindus indica* seeds. Eur J Int Med. 2020;40:101244. doi: 10.1016/j.eujim.2020.101244.
19. Cao H, Zhang W, Liu D, Hou M, Liu S, He W, *et al*. Identification, *In vitro* evaluation and modeling studies of the constituents from the roots of *Arnebia euchroma* for antitumor activity and STAT3 inhibition. Bioorg Chem. 2020;96:103655. doi: 10.1016/j.bioorg.2020.103655.
20. Liu H, Li G, Zhang B, Sun D, Wu J, Chen F, *et al*. Suppression of the NF-κB signaling pathway in colon cancer cells by the natural compound Riccardin D from *Dumortiera hirsute*. Mol Med Rep. 2018;17(4):5837-5843. doi: 10.3892/mmr.2018.8617.
21. Ahmed HH, El-Abhar HS, Hassanin EAK, Abdelkader NF, Shalaby MB. *Ginkgo biloba* L. leaf extract offers multiple mechanisms in bridling N-methylnitrosourea - mediated experimental colorectal cancer. Biomed Pharmacother. 2017;95:387-393. doi: 10.1016/j.biopha.2017.08.103.
22. Huang S, Zhao SM, Shan LH, Zhou XL. Antitumor activity of nervosine VII, and the crosstalk between apoptosis and autophagy in HCT116 human colorectal cancer cells. Chin J Nat Med. 2020;18(2):81-89. doi: 10.1016/S1875-5364(20)30009-1.
23. Jin H, Seo GS, Lee SH. Isoliquiritigenin-mediated p62/SQSTM1 induction regulates apoptotic potential through attenuation of caspase-8 activation in colorectal cancer cells. Eur J Pharmacol. 2018;841:90-97. doi: 10.1016/j.ejphar.2018.10.015.
24. Cao ZX, Yang YT, Yu S, Li YZ, Wang WW, Huang J, *et al*. Pogostone induces autophagy and apoptosis involving PI3K/Akt/mTOR axis in human colorectal carcinoma HCT116 cells. J Ethnopharmacol. 2017;202:20-27. doi: 10.1016/j.jep.2016.07.028.
25. Wang G, Wang YZ, Yu Y, Wang JJ. Inhibitory ASIC2-mediated calcineurin/NFAT against colorectal cancer by triterpenoids extracted from *Rhus chinensis* Mill. J Ethnopharmacol. 2019;235:255-267. doi: 10.1016/j.jep.2019.02.029.
26. Zhang LL, Zhan L, Jin YD, Min ZL, Wei C, Wang Q, *et al*. SIRT2 mediated antitumor effects of shikonin on metastatic colorectal cancer. Eur J Pharmacol. 2017;797:1-8. doi: 10.1016/j.ejphar.2017.01.008.
27. Li SY, Shang J, Mao XM, Fan R, Li HQ, Li RH, *et al*. Diosgenin exerts anti-tumor effects through inactivation of cAMP/PKA/CREB signaling pathway in colorectal

cancer. Eur J Pharmacol. 2021;908:174370. doi: 10.1016/j.ejphar.2021.174370.
28. Tian SH, Yang ZX, Zhang JQ, Yang F, Zhong LF, *et al*. Feng-liao-chang-wei-kang is synergistic with 5-fluorouracil in inhibiting proliferation of colorectal cancer. Asian Pac J Trop Med. 2019;12(14):41-53. doi: 10.4103/1995-7645.271979.
29. Egas V, Millan E, Collado JA, Ramirez-Apan T, Mendez-Cuesta CA, Munoz E, *et al*. Effect of natural and semi-synthetic cadinanes from *Heterotheca inuloides* on NF-κB, Nrf2 and STAT3 signaling pathways and evaluation of their *In vitro* cytotoxicity in human cancer cell lines. Bioorg Med Chem. 2017;25(12):3135-3147. doi: 10.1016/j.bmc.2017.03.069.
30. Zhang Y, He XZ, Yang H, Liu HY, An LK. Robustadial A and B from *Eucalyptus globulus* Labill. and their anticancer activity as selective tyrosyl-DNA phosphodiesterase 2 inhibitors. Phytother Res. 2021;35(9):5282-5289. doi: 10.1002/ptr.7207.
31. Qi L, Zhang Y, Zhang W, Wang Y, Han Y, Ding Y. The inhibition of colorectal cancer growth by the natural product macrocarpal I. Free Radic Biol Med. 2021;162:383-391. doi: 10.1016/j.freeradbiomed.2020.10.317.
32. Nasri I, Chawech R, Girardi C, Mas E, Ferrand A, Vergnolle N, *et al*. Anti-inflammatory and anticancer effects of flavonol glycosides from *Diplotaxis harra* through GSK3β regulation in intestinal cells. Pharm Biol. 2017;55(1):124-131. doi: 10.1080/13880209.2016.1230877.
33. Mericli F, Becer E, Kabadayi H, Hanoglu A, Yigit HD, Ozkum YD, *et al*. Fatty acid composition and anticancer activity in colon carcinoma cell lines of *Prunus dulcis* seed oil. Pharm Biol. 2017;55(1):1239-1248. doi: 10.1080/13880209.2017.1296003.
34. Gundogdu G, Dodurga Y, Elmas L, Tasci SY, Karaoglan ES. Investigation of the Anticancer Mechanism of Isoorientin Isolated from *Eremurus Spectabilis* Leaves via Cell Cycle Pathways in HT-29 Human Colorectal Adenocarcinoma Cells. Eurasian J Med. 2018;50:168-172. doi: 10.5152/eurasianjmed.2018.17403.
35. Zhao J, Xu J, Lv J. Identification of profilin 1 as the primary target for the anti-cancer activities of Furowanin A in colorectal cancer. Pharmacol Rep. 2019;71(5):940-949. doi: 10.1016/j.pharep.2019.05.007.
36. Kumar N, Biswas S, Hosur SA, Basu MS, Hipolith VM, Elizabeth MJ, *et al*. Pinocembrin enriched fraction of *Elytranthe parasitica* (L.) Danser induces apoptosis in HCT 116 colorectal cancer cells. J Infect Chemother. 2017;23(6):354-359. doi: 10.1016/j.jiac.2017.02.009.
37. Jisha N, Vysakh A, Vijeesh V, Latha MS. Ethyl acetate fraction of *Muntingia calabura* L. exerts anti-colorectal cancer potential via regulating apoptotic and inflammatory pathways. J Ethnopharmacol. 2020;261:113064. doi: 10.1016/j.jep.2020.113064.
38. Mahajan P, Gnana Oli R, Jachak SM, Bharate SB, Chaudhuri B. Antioxidant and antiproliferative activity of indigocarpan, a pterocarpan from *Indigofera aspalathoides*. J Pharm Pharmacol. 2016;68(10):1331-9. doi: 10.1111/jphp.12609.
39. Tang S, Cai S, Ji S, Yan X, Zhang W, Qiao X, *et al*. Isoangustone A induces autophagic cell death in colorectal cancer cells by activating AMPK signaling. Fitoterapia. 2021;152:104935. doi: 10.1016/j.fitote.2021.104935.
40. Kim WK, Bach DH, Ryu HW, Oh J, Park HJ, Hong JY, *et al*. Cytotoxic activities of *Telectadium dongnaiense* and its constituents by inhibition of the Wnt/β-catenin signaling pathway. Phytomedicine. 2017;34:136-142. doi: 10.1016/j.phymed.2017.08.008.
41. Mohammed HA, Abd El-Wahab MF, Shaheen U, Mohammed AEI, Abdalla AN, Ragab EA. Isolation, Characterization, Complete Structural Assignment, and Anticancer Activities of the Methoxylated Flavonoids from *Rhamnus disperma* Roots. Molecules. 2021;26(19):5827. doi: 10.3390/molecules26195827.
42. Ma Z, Bao X, Gu J. Furowanin A-induced autophagy alleviates apoptosis and promotes cell cycle arrest via inactivation STAT3/Mcl-1 axis in colorectal cancer. Life Sci. 2019;218:47-57. doi: 10.1016/j.lfs.2018.12.027.
43. Yoo E, Lee J, Lertpatipanpong P, Ryu J, Kim CT, Park EY, *et al*. Anti-proliferative activity of *A. Oxyphylla* and its bioactive constituent nootkatone in colorectal cancer cells. BMC Cancer. 2020;20(1):881. doi: 10.1186/s12885-020-07379-y.
44. Szoka L, Isidorov V, Nazaruk J, Stocki M, Siergiejczyk L. Cytotoxicity of Triterpene *Seco*-Acids from *Betula pubescens* Buds. Molecules 2019; 24(22): 4060. doi: 10.3390/molecules24224060.
45. Trinel M, Le Lamer AC, Jullian V, Jacquemin D, Graton J, Cristofoli V, *et al*. Daphnanes diterpenes from the latex of *Hura crepitans* L. And activity against human colorectal cancer cells Caco-2. Bioorg Chem 2020; 103: 104132. doi: 10.1016/j.bioorg.2020.104132.
46. Maiyo F, Moodley R, Singh M. Phytochemistry, cytotoxicity and apoptosis studies of b-sitosterol-3-*o*-glucoside and β -amyrin from *Prunus africana*. Afr J Tradit Complement Altern Med 2016; 13(4): 105-112. doi: 10.21010/ajtcam.v13i4.15.
47. Wang JT, Ge D, Qu HF, Wang GK, Wang G. Chemical constituents of *Curcuma kwangsiensis* and their antimigratory activities in RKO cells. Nat Prod Res. 2019;33(24):3493-3499. doi: 10.1080/14786419.2018.1484463.
48. Leong KH, Looi CY, Loong XM, Cheah FK, Supratman U, Litaudon M, *et al*. Cycloart-24-ene-26-ol-3-one, a New Cycloartane Isolated from Leaves of *Aglaia exima* Triggers Tumour Necrosis Factor-Receptor 1-Mediated Caspase-Dependent Apoptosis in Colon Cancer Cell Line. PLoS One. 2016;11(4):e0152652. doi: 10.1371/journal.pone.0152652.
49. Sharma N, Kumar A, Sharma PR, Qayum A, Singh SK, Dutt P, *et al*. A new clerodane furano diterpene glycoside from *Tinospora cordifolia* triggers autophagy and apoptosis in HCT-116 colon cancer cells. J Ethnopharmacol 2018; 211: 295-310. doi: 10.1016/j.jep.2017.09.034.
50. Zeng Q, Che Y, Zhang Y, Chen M, Guo Q, Zhang W. Thymol Isolated from *Thymus vulgaris* L. Inhibits Colorectal Cancer Cell Growth and Metastasis by Suppressing the Wnt/β-Catenin Pathway. Drug Des Devel Ther. 2020;14:2535-2547. doi: 10.2147/DDDT.S254218.
51. Pinto LC, Mesquita FP, Barreto LH, Souza PFN, Ramos INF, Pinto AVU, *et al*. Anticancer potential of limonoids from *Swietenia macrophylla*: Genotoxic, antiproliferative and proapoptotic effects towards human colorectal cancer. Life Sci. 2021;285:119949. doi: 10.1016/j.lfs.2021.119949.

52. Aissaoui H, Mencherini T, Esposito T, De Tommasi N, Gazzerro P, Benayache S, *et al*. *Heliotropium bacciferum* Forssk. (Boraginaceae) extracts: chemical constituents, antioxidant activity and cytotoxic effect in human cancer cell lines. Nat Prod Res. 2019;33(12):1813-1818. doi: 10.1080/14786419.2018.1437433.
53. Calibasi-Kocal G, Pakdemirli A, Bayrak S, Ozupek NM, Sever T, Basbinar Y, *et al*. Curcumin effects on cell proliferation, angiogenesis and metastasis in colorectal cancer. J BUON 2019; 24: 1482-1487.
54. Lee J, Kim YS, Lee J, Heo SC, Lee KL, Choi SW, *et al*. Walnut Phenolic Extract and Its Bioactive Compounds Suppress Colon Cancer Cell Growth by Regulating Colon Cancer Stemness. Nutrients. 2016;8(7):439. doi: 10.3390/nu8070439.
55. Wu KH, Lee WJ, Cheng TC, Chang HW, Chen LC, Chen CC, *et al*. Study of the antitumor mechanisms of apiole derivatives (AP-02) from *Petroselinum crispum* through induction of G0/G1 phase cell cycle arrest in human COLO 205 cancer cells. BMC Complement Altern Med. 2019;19(1):188. doi: 10.1186/s12906-019-2590-9.
56. Lee SH, Lee J, Herald T, Cox S, Noronha L, Perumal R, *et al*. Anticancer Activity of a Novel High Phenolic Sorghum Bran in Human Colon Cancer Cells. Oxid Med Cell Longev 2020; 2020: 2890536. doi: 10.1155/2020/2890536.
57. Jeong S, Yun HK, Jeong YA, Jo MJ, Kang SH, Kim JL, *et al*. Cannabidiol-induced apoptosis is mediated by activation of Noxa in human colorectal cancer cells. Cancer Lett. 2019;447:12-23. doi: 10.1016/j.canlet.2019.01.011.
58. Reddivari L, Charepalli V, Radhakrishnan S, Vadde R, Elias RJ, Lambert JD, *et al*. Grape compounds suppress colon cancer stem cells *In vitro* and in a rodent model of colon carcinogenesis. BMC Complement Altern Med. 2016;16:278. doi: 10.1186/s12906-016-1254-2.
59. Ye YL, Chang HS, Tseng YF, Shi LS. Suppression of IL-8 Release by Sweet Olive Ethanolic Extract and Compounds in WiDr Colon Adenocarcinoma Cells. J Food Sci. 2017;82(8):1792-1798. doi: 10.1111/1750-3841.13786.
60. Bi W, He CN, Li XX, Zhou LY, Liu RJ, Zhang S, *et al*. Ginnalin A from Kujin tea (*Acer tataricum* subsp. *ginnala*) exhibits a colorectal cancer chemoprevention effect via activation of the Nrf2/HO-1 signaling pathway. Food Funct. 2018;9(5):2809-2819. doi: 10.1039/c8fo00054a.
61. Wang Y, Shen JZ, Chan YW, Ho WS. Identification and Growth Inhibitory Activity of the Chemical Constituents from *Imperata Cylindrica* Aerial Part Ethyl Acetate Extract. Molecules. 2018;23(7):1807. doi: 10.3390/molecules23071807.
62. Ramadoss DP, Sivalingam N. Vanillin extracted from Proso and Barnyard millets induce apoptotic cell death in HT-29 human colon cancer cell line. Nutr Cancer 2020; 72(8): 1422-1437. doi: 10.1080/01635581.2019.1672763.
63. Moura AF, Lima KSB, Sousa TS, Marinho-Filho JDB, Pessoa C, Silveira ER, *et al*. *In vitro* antitumor effect of a lignan isolated from *Combretum fruticosum*, trachelogenin, in HCT-116 human colon cancer cells. Toxicol *In vitro*. 2018;47:129-136. doi: 10.1016/j.tiv.2017.11.014.
64. Paterna A, Gomes SE, Borralho PM, Mulhovo S, Rodrigues CM, Ferreira MU. (3'R)-hydroxytabernaelegantine C: A bisindole alkaloid with potent apoptosis inducing activity in colon (HCT116, SW620) and liver (HepG2) cancer cells. J Ethnopharmacol. 2016;194:236-244. doi: 10.1016/j.jep.2016.09.020.
65. Li Z, Mao L, Yu B, Liu H, Zhang Q, Bian Z, *et al*. GB7 acetate, a galbulimima alkaloid from *Galbulimima belgraveana*, possesses anticancer effects in colorectal cancer cells. J Pharm Anal 2021. doi: 10.1016/j.jpha.2021.06.007.
66. Son Y, An Y, Jung J, Shin S, Park I, Gwak J, *et al*. Protopine isolated from *Nandina domestica* induces apoptosis and autophagy in colon cancer cells by stabilizing p53. Phytother Res. 2019;33(6):1689-1696. doi: 10.1002/ptr.6357.
67. Paterna A, Gomes SE, Borralho PM, Mulhovo S, Rodrigues CM, Ferreira MU. Vobasinyl-Iboga Alkaloids from *Tabernaemontana elegans*: Cell Cycle Arrest and Apoptosis-Inducing Activity in HCT116 Colon Cancer Cells. J Nat Prod. 2016;79(10):2624-2634. doi: 10.1021/acs.jnatprod.6b00552.
68. Arun A, Patel OPS, Saini D, Yadav PP, Konwar R. Anti-colon cancer activity of *Murraya koenigii* leaves is due to constituent murrayazoline and O-methylmurrayamine A induced mTOR/AKT downregulation and mitochondrial apoptosis. Biomed Pharmacother. 2017;93:510-521. doi: 10.1016/j.biopha.2017.06.065.
69. Zhou J, Li Z, Zhang J, Wang H, Yin S, Du J. 8-Acetonyldihydronitidine inhibits the proliferation of human colorectal cancer cells via activation of p53. Eur J Pharmacol. 2019;854:256-264. doi: 10.1016/j.ejphar.2019.03.042.
70. Tian J, Mo J, Xu L, Zhang R, Qiao Y, Liu B, *et al*. Scoulerine promotes cell viability reduction and apoptosis by activating ROS-dependent endoplasmic reticulum stress in colorectal cancer cells. Chem Biol Interact. 2020;327:109184. doi: 10.1016/j.cbi.2020.109184.
71. Baghdadi MA, Al-Abbasi FA, El-Halawany AM, Aseeri AH, Al-Abd AM. Anticancer Profiling for Coumarins and Related *O*-Naphthoquinones from *Mansonia gagei* against Solid Tumor Cells *In vitro*. Molecules 2018; 23(5): 1020. doi: 10.3390/molecules23051020.
72. Kuete V, Omosa LK, Tala VR, Midiwo JO, Mbaveng AT, Swaleh S, *et al*. Cytotoxicity of Plumbagin, Rapanone and 12 other naturally occurring Quinones from Kenyan Flora towards human carcinoma cells. BMC Pharmacol Toxicol. 2016;17(1):60. doi: 10.1186/s40360-016-0104-7.
73. Li X, Chen M, Yao Z, Du H, Zhang T, Wang H, *et al*. Jujuboside B induces mitochondrial-dependent apoptosis in colorectal cancer through ROS-mediated PI3K/Akt pathway *In vitro* and *In vivo*. J Funct Foods. 2021;87:104796. doi: 10.1016/j.jff.2021.104796.
74. Ha SH, Kwon KM, Park JY, Abekura F, Lee YC, Chung TW, *et al*. Esculentoside H inhibits colon cancer cell migration and growth through suppression of MMP-9 gene expression via NF-kB signaling pathway. J Cell Biochem. 2019;120(6):9810-9819. doi: 10.1002/jcb.28261.
75. Chang L, Zhou R, He Y, Meng M, Hu J, Liu Y, *et al*. Total saponins from *Rhizoma Panacis* Majoris inhibit proliferation, induce cell cycle arrest and apoptosis and influence MAPK signalling pathways on the colorectal

cancer cell. Mol Med Rep. 2021;24(2):542. doi: 10.3892/mmr.2021.12181.
76. Gajendran B, Durai P, Madhu Varier K, Chinnasamy A. A novel phytosterol isolated from *Datura inoxia*, RinoxiaB is a potential cure colon cancer agent by targeting BAX/Bcl2 pathway. Bioorg Med Chem 2020; 28(2): 115242. doi: 10.1016/j.bmc.2019.115242.
77. Yao M, Li R, Yang Z, Ding Y, Zhang W, Li W, *et al*. PP9, a steroidal saponin, induces G2/M arrest and apoptosis in human colorectal cancer cells by inhibiting the PI3K/Akt/GSK3β pathway. Chem Biol Interact. 2020;331:109246. doi: 10.1016/j.cbi.2020.109246.
78. Kruakaew S, Seeka C, Lhinhatrakool T, Thongnest S, Yahuafai J, Piyaviriyakul S, *et al*. Cytotoxic Cardiac Glycoside Constituents of *Vallaris glabra* Leaves. J Nat Prod. 2017;80(11):2987-2996. doi: 10.1021/acs.jnatprod.7b00554.
79. Alam F, Najum Us Saqib Q, Waheed A. Cytotoxic activity of extracts and crude saponins from *Zanthoxylum armatum* DC. against human breast (MCF-7, MDA-MB-468) and colorectal (Caco-2) cancer cell lines. BMC Complement Altern Med. 2017;17:368. doi: 10.1186/s12906-017-1882-1.
80. Sriyatep T, Tantapakul C, Andersen RJ, Patrick BO, Pyne SG, Muanprasat C, *et al*. Resolution and identification of scalemic caged xanthones from the leaf extract of *Garcinia propinqua* having potent cytotoxicities against colon cancer cells. Fitoterapia. 2018;124:34-41. doi: 10.1016/j.fitote.2017.10.009.
81. Sriyatep T, Andersen RJ, Patrick BO, Pyne SG, Muanprasat C, Seemakhan S, *et al*. Scalemic Caged Xanthones Isolated from the Stem Bark Extract of *Garcinia propinqua.* J Nat Prod. 2017;80(5):1658-1667. doi: 10.1021/acs.jnatprod.7b00240.
82. Wang N, Zhou F, Guo J, Zhu H, Luo S, Cao J. Euxanthone suppresses tumor growth and metastasis in colorectal cancer via targeting CIP2A/PP2A pathway. Life Sci. 2018;209:498-506. doi: 10.1016/j.lfs.2018.08.052.
83. Lin S, Fu P, Chen T, Ye J, Yang XW, Zhang WD. Three minor valepotriate isomers from *Valeriana jatamansi* and their cytotoxicity. J Asian Nat Prod Res. 2017;19(1):15-21. doi: 10.1080/10286020.2016.1258065.
84. Tan YZ, Peng C, Hu CJ, Li HX, Li WB, He JL, *et al*. Iridoids from *Valeriana jatamansi* induce autophagy-associated cell death via the PDK1/Akt/mTOR pathway in HCT116 human colorectal carcinoma cells. Bioorg Chem. 2019;87:136-141. doi: 10.1016/j.bioorg.2019.03.020.
85. Bartnik M, Slawinska-Brych A, Zurek A, Kandefer-Szerszen M, Zdzisinska B. 8-methoxypsoralen reduces AKT phosphorylation, induces intrinsic and extrinsic apoptotic pathways, and suppresses cell growth of SK-N-AS neuroblastoma and SW620 metastatic colon cancer cells. J Ethnopharmacol. 2017;207:19-29. doi: 10.1016/j.jep.2017.06.010.
86. Asif M, Yehya AHS, Dahham SS, Mohamed SK, Shafaei A, Ezzat MO, *et al*. Establishment of *In vitro* and *In vivo* anti-colon cancer efficacy of essential oils containing oleo-gum resin extract of *Mesua ferrea*. Biomed Pharmacother. 2019;109:1620-1629. doi: 10.1016/j.biopha.2018.10.127.
87. Park EJ, Sang-Ngern M, Chang LC, Pezzuto JM. Induction of cell cycle arrest and apoptosis with downregulation of Hsp90 client proteins and histone modification by 4β-hydroxywithanolide E isolated from *Physalis peruviana.* Mol Nutr Food Res. 2016;60(6):1482-500. doi: 10.1002/mnfr.201500977.
88. Pedrosa LF, Lopes RG, Fabi JP. The acid and neutral fractions of pectins isolated from ripe and overripe papayas differentially affect galectin-3 inhibition and colon cancer cell growth. Int J Biol Macromol. 2020;164:2681-2690. doi: 10.1016/j.ijbiomac.2020.08.135.
89. Abalos NN, Ebajo VD Jr, Camacho DH, Jacinto SD. Cytotoxic and Apoptotic Activity of Aglaforbesin Derivative Isolated from *Aglaia loheri* Merr. on HCT116 Human Colorectal Cancer Cells. Asian Pac J Cancer Prev. 2021;22(1):53-60. doi: 10.31557/APJCP.2021.22.1.53.
90. Asif M, Shafaei A, Jafari SF, Mohamed SK, Ezzat MO, Abdul Majid AS, *et al*. Isoledene from *Mesua ferrea* oleo-gum resin induces apoptosis in HCT 116 cells through ROS-mediated modulation of multiple proteins in the apoptotic pathways: A mechanistic study. Toxicol Lett 2016; 257: 84-96. doi: 10.1016/j.toxlet.2016.05.027.
91. Chen L, Wang WL, Song TF, Xie X, Ye XW, Liang Y, *et al*. Anti-colorectal cancer effects of tripolinolate A from *Tripolium vulgare*. Chin J Nat Med. 2017;15(8):576-583. doi: 10.1016/S1875-5364(17)30085-7.
92. Ahmad R, Sahidin I, Taher M, Low C, Noor NM, Sillapachaiyaporn C, *et al*. Polygonumins A, a newly isolated compound from the stem of *Polygonum minus* Huds with potential medicinal activities. Sci Rep. 2018;8(1):4202. doi: 10.1038/s41598-018-22485-5.
93. Zhu X, Ouyang W, Pan C, Gao Z, Han Y, Song M, *et al*. Identification of a new benzophenone from *Psidium guajava* L. leaves and its antineoplastic effects on human colon cancer cells. Food Funct. 2019;10:4189-4198. doi: 10.1039/c9fo00569b.
94. Jose A, Elango K, Madhunapantula SV, Raghavamenon AC. Tricaproin isolated from *Simarouba glauca* inhibit colorectal cancer cell growth: A mechanistic approach *In vitro* and *In vivo*. Mater Today: Proc. 2020;33(5):2193-2202. doi: 10.1016/j.matpr.2020.04.015.