



**International Journal of Biology, Pharmacy
and Allied Sciences (IJBPAS)**

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

**PLANTS AND PHYTOCHEMICALS IN THE TREATMENT OF COLORECTAL
CANCER: RECENT UPDATES**

**MANDAL SK^{1*}, BISWAS D¹, SONY A¹, DE A¹, DASTIDER D², BAIDYA M², PAUL
S², DAWN S¹ AND MANDAL S³**

1: Department of Pharmaceutical Chemistry, Dr. B. C. Roy College of Pharmacy and Allied Health Sciences, Durgapur, West Bengal-713206, India

2: Department of Pharmaceutical Technology, Brainware University, 398-Ramkrishnapur Road, Barasat, Kolkata-700125, West Bengal, India

3: Bengal College of Pharmaceutical Science and Research, Durgapur, West Bengal-713212, India

***Corresponding Author: Dr. Sudip Kumar Mandal: E Mail: gotosudip79@gmail.com;**

Contact no.:+91-8670192100

Received 24th Nov. 2020; Revised 30th Dec. 2020; Accepted 8th Jan. 2021; Available online 1st Oct. 2021

<https://doi.org/10.31032/IJBPAS/2021/10.10.5657>

ABSTRACT

Colorectal cancer (CRC) is one of the leading causes of mortality. The standard treatment for CRC and other cancer is generally based on using cytotoxic drugs, radiotherapy, chemotherapy, and surgery. However, the use of traditional treatments has received attention in recent years. Chemo resistance, adverse effects and disease recurrence are big challenges in the discovery of anticancer drugs. Literature review demonstrates that plant derived chemicals significantly reduced incidence rate of CRC. Plant derived chemical agents act as a prominent source of novel compounds for CRC drug discovery. Phytochemicals have been the focus of an increasing number of studies due to their ability to modulate carcinogenic processes through the alteration of multiple cancer cell survival pathways. The aim of the current review is to provide an overview of medicinal plants and their phytochemicals effective on colorectal cancer with underlying mechanisms of action. A Web of Science, PubMed, Google Scholar and Science Direct search was performed for relevant articles.

Keywords: Colorectal cancer, plant, phytochemical, apoptosis, cell cycle arrest

INTRODUCTION

Cancer is the second leading cause of death worldwide [1-3]. According to World Health Organization (WHO) report, colorectal cancer (CRC) was third most commonly diagnosed cancer (1.8 million cases reported) and second most common in mortality (0.88 million cases reported) among all cancers in 2018 [4]. According to recent assumption, within 2030 colorectal cancer incidence will increase by 60% worldwide [5]. Colorectal cancer is the result of a progressive accumulation of genetic and epigenetic alterations leading to marked genomic instability [6]. Among colorectal cancer incidences, only 10% are inherited but most of cases are sporadic i.e. patients with no family history [7]. Rather it evolves slowly over years through multistep processes; first normal mucosa is converted into adenomatous polyps which then modify into invasive carcinoma. Lifestyle manifests great influence on cancer incidence mainly on CRC. Almost 70% of colorectal cancer cases are connected to diet [8]. There are also several risk factors associated with CRC include obesity, alcohol intake, consumption of red meat, processed food, lack of physical activity. On the other hand, increased physical activity, post-menopausal hormone therapy, vegetable and fruit intake, selenium and folate rich food consumption reduce the risk of CRC

incidence [9]. In this context, medicinal plants provide a large number of chemicals with proven cytotoxicity [10, 11] and apoptogenic activity against colorectal cancer [12, 13]. Because of their safety and affordability, these agents from nature provide a novel opportunity for treatment of colorectal cancer, an 'old age' disease with 'age old' solution [8].

MEDICINAL PLANTS

***Curcuma longa*:** *C.longa* is a well-known traditional medicinal herb, originated from India, belongs to family Zingiberaceae. It is a rhizomatous perennial herb, now cultivated throughout tropical countries for spices and medicinal purposes [14]. Curcumin, a natural polyphenol, is the main phytochemical, extracted from the rhizome of *C.longa* [15]. Recently, Curcumin is under clinical trial [16]. According to recent studies, curcumin has diverse pharmacological properties like anti-microbial, anti-inflammatory, free radical scavenging; specifically, curcumin showed marked anti-neoplastic activity [17]. Four human colorectal cancer lines i.e. HT29, HT15, HCT116, DLD1 were treated with ethanolic extract of *C.longa*, growth inhibition was observed in a dose and time dependent manner [18]. HT29 and HT116 cell lines were inhibited at IC_{50} 11.67 μ g/ml, 9.42 μ g/ml respectively. Upon curcumin treatment, the cellular viability

and proliferation of human colon adenocarcinoma cell line were significantly inhibited in a dose and time dependent manner. Additionally, there were no cytotoxic effects on normal cells upon curcumin treatment. Rather it halted cell cycle at G₁ phase which resulted in reduction of cell population in S phase and induced apoptosis in p53 mutated COLO 320 DM cells [19, 20]. Curcumin inhibited proliferation of human colorectal cancer cell line CaCo-2 by inducing apoptosis via an increase in Bax/Bcl-2 ratio and activation of caspase-3/7 [21].

***Panax quinquefolius*:** *P. quinquefolius*, also known as American ginseng, is an herbaceous perennial plant, native to North America, China, belongs to Auraliaceae family. Ginseng plant has been used in traditional medicine system in oriental countries for thousand years [22]. Ginsenosides, the triterpenoid saponins, were isolated from dried roots, main bioactive compound, with proven anti-inflammatory action which plays crucial role in CRC prevention [23]. Several studies have been carried out to explore the effect of American ginseng in colorectal cancer mostly on cell lines. Treatment of American ginseng root extract with HCT116 and SW480 colorectal cancer cell lines induced mitochondrial damage and apoptosis [24]. It enhances anti-cancer effect by inactivating NF-kB [25]. In

another study, HT29 cell lines were treated with BST204, a fermented ginseng extract. It results in cell cycle arrest at G₁ phase accompanied by alteration of tumor gene expression: up regulation of p53, CDK inhibitor and down regulation of the proteins responsible for G₁-S transition i.e. CDK2, cyclin E and cyclinD1 [26]. However inhibition mechanism of ginseng is not very clear, previous studies indicated anti-inflammation and apoptosis as the most probable mechanism. Ginseng herb produced apoptosis via two pathways; intrinsic mitochondrial mediated pathway in which membrane permeability of mitochondria is organized and caspase-3, 9 is activated and extrinsic death receptor mediated pathway; promotes death receptor DR4 expression. Ginseng played crucial role in inflammation suppression via inhibition of COX-2 expression by inactivation of NF-kB [25].

***Garcinia mangostana*:** *Garcinia mangostana*, a tropical tree, popularly known as “Queen of fruits”, belongs to the family Clusiaceae. This plant is native to south-east Asia rainforest and cultivated for centuries. Now it can be found in several other countries throughout the world. Pericarp of this fruit has been used in traditional medicine in south-east Asian countries for several purposes from very old time [27]. According to phytochemical study, xanones (specifically α -mangostin

and γ -mangostin) are the main bio-active compounds, isolated from mangosteen fruit. Recent experiments exhibited that xanthenes have diverse pharmacological property i.e. anti-oxidant, anti-bacterial, cardioprotective, anti-inflammatory, anti-cancer [28] [29]. To analyze the effect of xanthone extract of mangosteen fruit on colorectal cancer, several experiments have been performed, mostly on cell lines. HCT116 colorectal cancer cell line was treated with xanthone extract containing α -mangostin (81%) and γ -mangostin (16%), dose dependent cytotoxicity was observed at $IC_{50}=6.5\pm 1.0 \mu\text{g/ml}$. Xanthone extract increased activity of caspase- 3, 9 but not of caspase-8 in cell line cells at 10 and 20 $\mu\text{g/ml}$ after 90 min of treatment. Most possible mechanism of cytotoxicity of xanthone extract containing α -mangostin and γ -mangostin is induction of apoptosis through intrinsic mitochondrial mediated pathway. These compounds caused upregulation of MAPK/ERK pathway and enhanced pro-apoptotic effect of p53 tumor suppressor gene and suppressed the NF-kB pathway [30]. In another study, HT29 cell line was used and upon γ -mangostin treatment more than fifty percent cytotoxicity was reported within 24 hr with IC_{50} dose ($68.48 \pm 6.73 \mu\text{M}$). γ -Mangostin caused suppression of proliferation via apoptosis of that cells in a dose and time dependent manner [31]. Xanthone extract

from the pericarp of the fruit was tested over DLD1 human colorectal cancer cells. Anti-proliferative effect was noticed with IC_{50} dose of α -mangostin ($7.5 \mu\text{M}$) and γ -mangostin ($7.1 \mu\text{M}$). α -Mangostin caused cell cycle arrest at G_1/S phase and induced apoptosis via intrinsic pathway in DLD1 cells while γ -Mangostin halted cell cycle at S phase [32].

***Emilia sonchifolia*:** *Emilia sonchifolia*, also known as lilac tassel flower, is used as folk medicine in India and China. This herbaceous plant, belongs to Compositae family, is native to Asia though found all over the world. It is used to treat inflammation, wound, cough, and rheumatism [33] [34]. Previous experiments suggested that methanolic extract of *Emilia sonchifolia* has anti-oxidant, anti-inflammatory, anti-cancer property [35]. GC-MS analysis of *Emilia sonchifolia* extract reported that γ -humulene, a monocyclic sesquiterpene, was one of the major phytochemical [36]. Several studies have been performed to study the anti-colorectal cancer effect and possible mechanism of action of γ -humulene. In a study HT29 human colorectal cancer cell line was treated with *Emilia sonchifolia* extract and cell viability was markedly reduced in a dose dependent manner with IC_{50} of $53.67\pm 2.99 \mu\text{M}$ after 24 hr of treatment. Cell viability was decreased due to induction of apoptosis in the cells.

Apoptosis was confirmed by morphological study after 24 hr incubation which was evaluated by flow cytometric study. γ -Humulene increased the activity of caspase 8 and caspase 3. The component also increased the expression of DR5 protein which played key role in apoptic cell death. This result suggested that γ -humulene induced cell death in HT29 cells by apoptosis via extrinsic pathway mediated by death receptor [36]. In another study anti-colorectal cancer effect of the compound was explored where HCT116 human colorectal cancer cell line was treated with methanolic extract of *Emilia sonchifolia*. Upon treatment, more than 50% reduction of cell viability was reported with IC₅₀ dose of 50 μ g/ml after 24hr exposure. The extract decreased the cell viability in a dose dependent manner and causes apoptic morphological changes. Methanolic extract also enhanced the activity of caspase 3, caspase8 and caspase9 which are responsible for inducing apoptosis. This result collectively suggest that methanolic extract of *Emilia sonchifolia* accomplished cell death of HCT116 cells by inducing apoptosis via both extrinsic and intrinsic pathway and upregulation of p53 tumor suppressor gene. The Intrinsic pathway altered mitochondrial membrane permeability and increased the activity of caspase 3 and caspase 9 whether

extrinsic pathway involved death receptors and caspase 3 and caspase 8 [37].

***Rabdosia rubescens*:** *Rabdosia rubescens*, is an herb native to China, belongs to Labiatae family. The herb is used in traditional Chinese medicine for long time to manage health problems like sore throat, pharyngitis, digestive problems. Healthy tea prepared from leaves of the herb is very familiar among Chinese to clear throat and lungs [38]. This plant contains diterpenoids, flavonoids, triterpenoids, phenolic acids, volatile oil. But among them oridonin is the mainly responsible for anti-tumor action [39]. To study the pharmacological action of oridonin in CRC, human colorectal cancer cell lines HCT116, SW620, SW480, LoVo were treated with oridonin for 48hr. MTT assay ascertained that oridonin inhibited cell proliferation and induced apoptic cell death in a dose dependent manner in that cells. Additionally, it was found that the effect of oridonin was better on HCT 116 and LoVo cells than the others. Molecular study exposed that oridonin activated caspase 9, caspase 3 and two key protein of apoptic cell death process [40]. In another study, HCT 116, HT 29, SW 116 human colorectal cancer cell lines were used to study the most probable anti-colorectal cancer effect. Cell proliferation of these cells was inhibited by dose and time dependent manner. Among three cell lines HT 29 showed most

sensitivity to oridonin. Oridonin caused suppression of proteins related to G₂/M phase which lead G₂ arrest. These results established that cellular proliferation was accomplished by cell cycle arrest and apoptosis [41].

Olea europaea var. Sylvestris: *Olea europaea var. Sylvestris*, belongs to Oleracea family is the wild variety of olive trees which is native to mediterrian basin. Leaves of this plant are widely utilised in traditional European medicine system for a long time where it is used to treat diabetic problem, diuretic problem, or as anti-oxidant [42]. Phytochemical study exposed that several phenolic compounds are present in extract of leaves and fruits which are responsible for its strong anti-oxidant potential [43] [44]. Interestingly chance of mortality from colorectal disorder is much lower among people living in mediterrian basin due to regular consumption of this fruit, exhibits strong anti-inflammatory effect, which is part of so called mediterrian diet [45]. Several phenolic compounds were extracted which were reported to be cytotoxic [46]. To study the anti-colorectal cancer activity, extract of oleaster leaves which is rich in polyphenols was administered upon HCT 116 cell transplanted nude mice. The extract downgraded the tumor growth significantly and showed cytotoxicity at IC₅₀ 20 µg/ml. Here, phenolic extract

treatment induced apoptosis in cancer cells via caspase-3 activation [47]. Several studies suggested that among phenolic compounds, oleuropin may be responsible for anti-neoplastic effect. Human colorectal cancer cell lines HT29, SW260 were treated with oleuropin and after 72hr proliferation was inhibited markedly. Here apoptosis was induced by the molecule by upregulating p53 gene and reducing the expression of HIF-1α which leads to inhibition of cell proliferation [48].

Hylomecon vernalis: *Hylomecon vernalis*, is a medicinal herb, native to East Asia, found in mountain region of China and Korea, belongs to papaveraceae family. From very old time the herb is a part of Chinese folk medicine. It is used to relief from arthritis, rheumatic problem, neuralgia, skin problems [49]. Several analytical studies on phytochemicals revealed that various alkaloidal compounds present in the extract of aerial part which are responsible for anti-tumor, anti-inflammatory actions. Isolation of more than twenty phenolic compounds by column chromatography is reported which showed potent cytotoxicity against four human tumor cell lines [50]. Human colorectal cancer cell lines HT29, SW620 were treated with ethanolic extract of *H.vernalis* to analyze the anti-colorectal cancer effect. These results in successful inhibition of cellular proliferation of HT29,

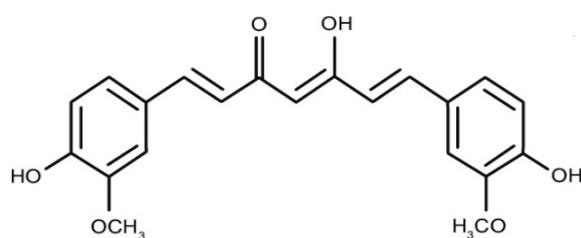
SW620 cells with IC_{50} of 0.10mg/ml, 0.14 mg/ml. Western blot analysis reported that apoptosis was induced by the extract by increasing caspase-3,9 expression and reduction of Bcl-2 expression which causes cell cycle arrest at G_1 [51]. This activity may be due to presence of berberin in the extract which is an alkaloidal compound. In another study berberine was administered to HCT 8 human colorectal cancer cell line in various concentrations. HCT 8 cell growth was inhibited by the compound in a dose and time dependent manner. Flow cytometry analysis suggested that berberin arrested cell cycle at S phase and induced apoptosis. Further study reported that apoptosis was induced by extrinsic pathway which is associated with p53 gene [52, 53]. To study the cytotoxicity HCT116, DLD1 cell lines were treated with berberine. It resulted in reduction of cell viability of HCT116 and DLD1 cells with IC_{50} of 80 and 200 μ M. Here berberin triggered autophagy by increasing the expression of GRP78 which is an autophagy inducer through ATF6 transcription factor activation [54].

Aloe vera: Among the 400 species of *Aloe*, *Aloe barbadensis*, *Aloe arborescens* are the most familiar ones, belong to Liliaceae family [55]. *Aloe vera* has been widely used in traditional Indian medicine system for 2000 yrs mainly in ayurveda and known as 'Ghrita kumari' [56]. So far 75 active

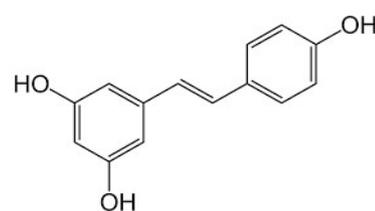
compounds have isolated from exodus of *Aloe* which include polysaccharides, phenolic compounds, enzymes, organic acids etc [57]. Based on traditional use and recent pharmacological and toxicological research, *Aloe vera* possessed diverse therapeutic properties which include anti-inflammatory, anti-tumor, anti-microbial, immunomodulatory, wound healing, hepatoprotective, anti-diabetic, anti-hyperlipidemic, anti-ulcer [58]. Among the active compounds aloin, aloe-emodin showed potent antioxidant property which took part in free radical mediated inflammatory reactions. Recent studies project aloin as potent molecule for the treatment of cancer due to its anti-proliferation, anti-angiogenesis potential [59]. HT29 human colorectal cancer cell line was taken to study the effect of aloin and aloe-emodin and cell-viability after 24 hr. Aloe-emodin suppressed cell viability at 10 μ M whereas aloin showed at 50 μ M. In this experiment aloe-emodin was most potent molecule which was able to reduce cell vitality up to 75.6% only at 10 μ M and IC_{50} value was 42.1 μ M. This result exhibited that aloe-emodin suppressed cell viability in a dose and time depended manner. In other studies aloin showed its anti-cancer potential by suppressing cell-proliferation, angiogenesis [60]. In another study human colorectal cancer cells SW480 and SW620 were treated with emodin in

DMSO solution. Accordance the findings analyzers, emodin produced cytotoxicity in a time and concentration dependent manner. The IC_{50} value for SW480 and SW620 at 24 hr was $66 \pm 2.3 \mu\text{M}$ and $56 \pm 3.3 \mu\text{M}$. Effect of emodin on Wnt/ β -catenin signalling pathway of CRC cells was also clarified by TOPFlash/FOPFlash luciferase reporter assay. The result showed that emodin suppressed transcriptional activity

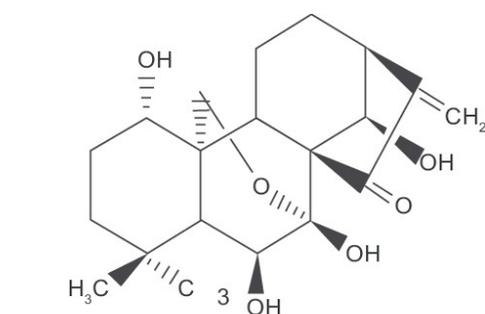
of β -catenin by suppressing Wnt/ β -catenin signalling pathway. Emodin exerted anti-cancer effect by generating reactive oxygen species (ROS) too. Upon accumulation of ROS, migration and growth of tumour cells get arrested but not viability. Through Inhibition on Wnt signalling pathway, cytotoxic effect made emodin an important moiety for CRC treatment [61].



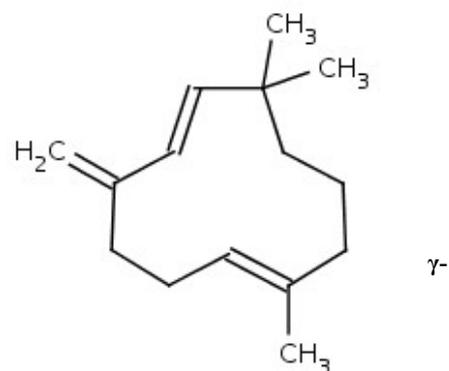
Curcumin



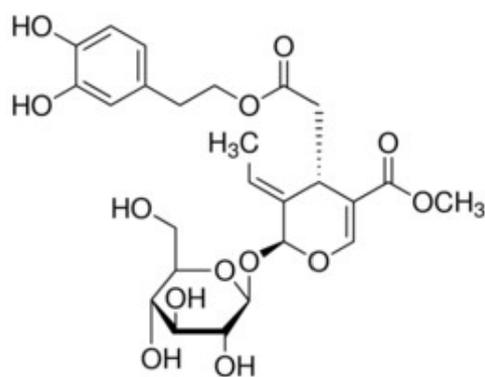
Resveratrol



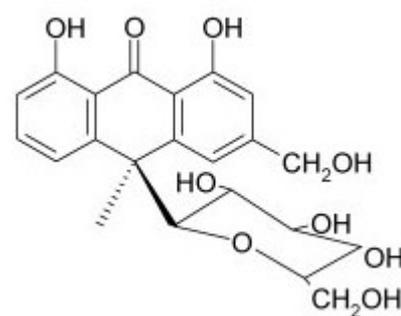
Oridonin



humulene



Oleuropin



Aloin

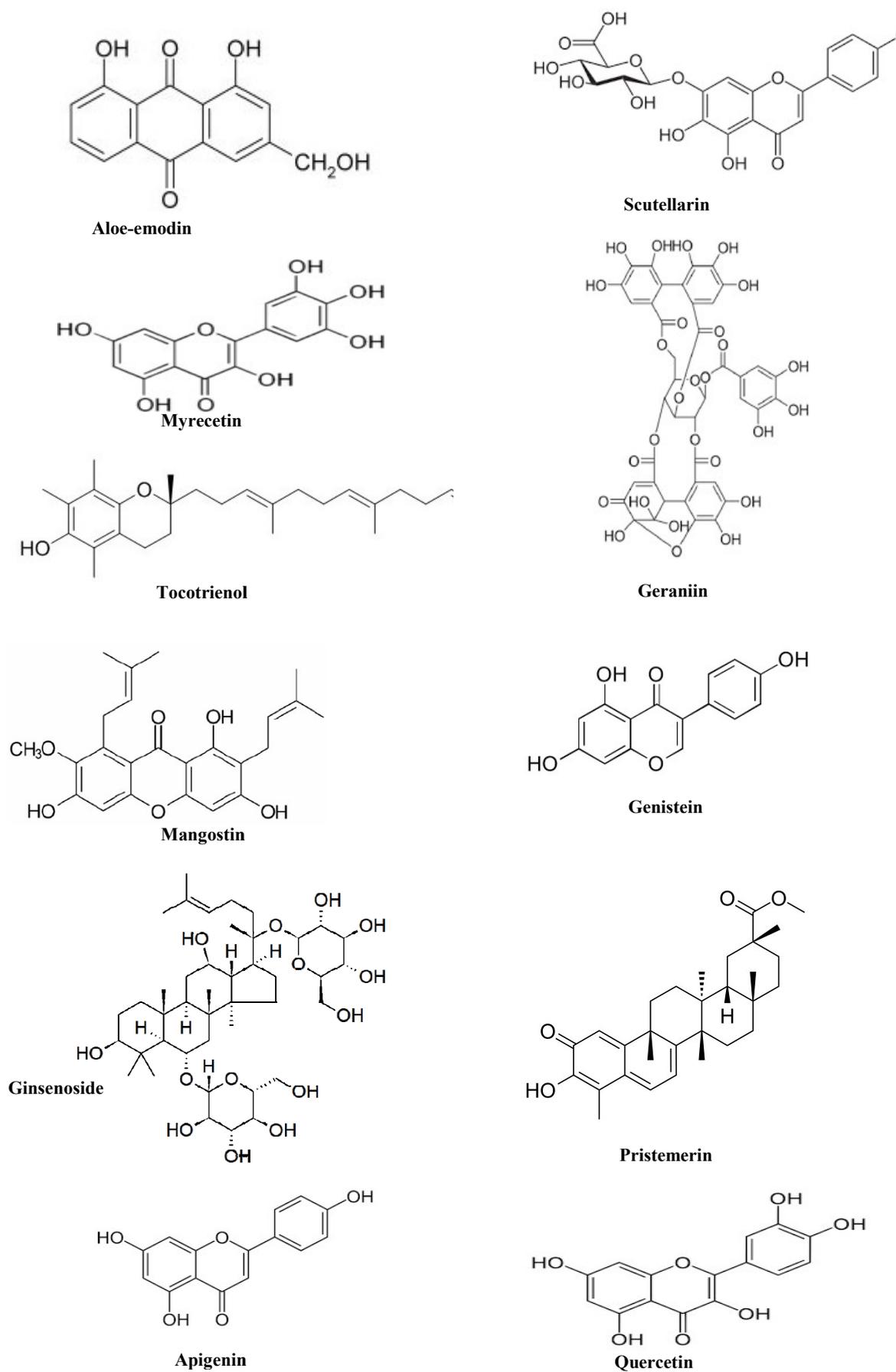


Figure 1: Phytochemicals used in CRC

PHYTOCHEMICALS

Scutellarin: Scutellarin is a flavonoid obtained from a medicinal herb *Scutellaria barbata* and it showed proapoptotic effect on HCT116 human colon cancer. It showed anti-proliferative, anti-metastatic, apoptotic, anti-invasion, anti-angiogenic effect *in vitro* and *in vivo* [62]. Scutellarin along with resveratrol and 5-fluorouracil prevented the growth of colorectal cancer cells by increasing the caspase-6 activation. Human colon cancer cells were kept in a different concentration of scutellarin. Growth of cells and necrobiosis were decided by western blot analysis, MTT assay (which is a type of colorimetric assay used for the determination of cell metabolic activity) or TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) staining, and other assays. Treatment with scutellarin decreased the growth of HCT116 cells in a dose and time dependent manner. TUNEL staining also showed that scutellarin activated the cell death in HCT116 cells. Scutellarin reduced the function of HTC-116 in a time and dose dependent manner [62, 63]. The expression level of the anti-apoptotic protein i.e Bcl 2 apoptosis regulator, was shorten by scutellarin in HCT116 cells, whereas the expression Bcl2 associated X apoptosis regulator (Bax) and the activation of caspase-3.lprotein were increased by

scutellarin treatment. Scutellarin also reduced the growth and activate apoptosis of human colon carcinoma cells by regulating p53 and Bcl2/Bax expression [64-66].

Myrecetin: 3,5,7,3',4',5'-hexahydroxyflavonecannabiscetin also known as myrecetin is a type of bioflavonoid found in medicinal plants, wines, vegetables, tea. It was isolated from *Myricanabi thunb* [67]. It is a lipophilic compound thus has low solubility but can be solubilized in organic compound such as acetone, dimethylformamide. It acted as a anti-carcinogen and chemo preventive agent. Myrecetin also inhibited the growth of HTC15 human colorectal cancer cells. It showed cytotoxicity and DNA condensation in dose dependent manner in human colorectal cell lines. It increased the BCL-2 associated X protein [68-70].

Geraniin: Geraniin is a dehydroellagitannin found in geraniums. It was found in *Geranium thunbergii* belong to family Sapindaceae, Gereniaceae and Elaeocarpaceae [71]. Geraniin showed high anti-cancer activity [72]. Geraniin affected the spindle assembly checkpoint (SAC) of HCT116 colorectal cancer cell lines. SAC is a kind of checkpoint during the cell cycle that prevents the separation of duplicated chromosomes until the chromosomes get attached to the spindle. When the HTC116 treated with geraniin the growth of cancer

cells decreased and also caused cell death in mitotic and premitotic HTC116 cells. It decreased the transcriptional expression of several SAC kinases which weakens the function of SAC on HCT116 cells which caused mitotic aberration [73]. According to the literature, when cells were exposed to different concentration of geraniin (25, 50 and 100 $\mu\text{g/ml}$) for 24 to 48 hrs, results showed induction of apoptosis on colo205 and colo320 cancer cell lines. It also increased chromosomal instability which helped in decrease of growth of cancer cell lines [74].

Tocotrienol: Tocotrienol is a fat soluble Vitamin E compound. The main sources of tocotrienol are palm oil, rice bran oil, palm kernel oil [75, 76]. Tocotrienol prevent metastasis, cell proliferation on colorectal cancer cells [77]. Tocotrienol which are found in palm oil fraction are known as tocotrienol rich fraction (TRF) [75]. According to research, after feeding TRF for two weeks, Balb/c nude mice were inoculated human colon SW620 neoplastic cell, continued to feed TRF for four weeks. The results showed that TRF considerably suppressed the expansion of xenografts in nude mice, additionally affected the activity of antioxidative enzymes within the liver tissue of mice [77].

Saponin: Saponins was extracted from Liliaceae family herbs. It showed anti-

cancer activity with low or no toxicity. Paris Saponin VII (PSVII), derived from *Trillium tschonoskii* Maxim, was tested on SW-620 and HT-29 human colorectal cancer cell lines. It showed that PSVII stopped the growth of colorectal cancer cell lines in dose dependent manner [78]. PSVII also showed anti-metastatic activity on colorectal cancer cell lines. It was determined by performing western blot analysis and gelatin zymography assay [79]. Sulphated saponins from *Holothuria moebii* showed apoptosis in colorectal cancer cell. According to literature sulphated saponins had IC_{50} values ranging from 1.04 to 4.08 μM . [80].

Genistein: Genistein, an aniso-flavonoid, was derived from soyabean showed cell proliferation on human colorectal cell lines. The activity of genistein was tested on HTC-116 and LoVo colorectal cell lines. The cell proliferation was measured by using MTT assay and apoptosis was measured by flow cytometry [81, 82].

Resveratrol: Resveratrol (*trans*-3, 4', 5-trihydroxystilbene), a stilbenoid, was extracted from Chinese herbal medicine *Polygonum cuspidatum*. It also found in red wine, grapes, berries and peanuts. Resveratrol suppressed the metastasis and invasion of human CRC [83, 84]. Resveratrol down-regulated MALAT1 or NEAT2, which resulted in decreasing or reducing the nuclear localization of β -

catenin, thus disabled Wnt/ β -catenin signaling, which leads to the suppression of CRC invasion and metastasis [84]. Resveratrol might suppressed the epithelial to mesenchymal transition (EMT) in CRC through TGF- β 1/Smads signaling pathway that was mediated by Snail/E-cadherin expression [85]. Recently, resveratrol is under clinical trial [86, 87].

Pristimerin: Pristimerin is a triterpenoid which showed a cytotoxic effect on several cancer cell lines. It shows a great effect on colorectal cancer. Pristimerin was found to have strong and influential cytotoxic and proliferation inhibitory effects against three types of colon cancer cell lines specifically HCT-116, COLO-205 and SW-620. According to research, pristimerin triggered apoptosis in a dose dependent manner. Western blot test demonstrated that apoptotic method of pristimerin was related with caspase-3, caspase-8, PARP-1 [88]. HCT-116 xenograft model applied for investigating *in vivo* antitumor exercise of pristimerin. The results showed that pristimerin intrude with *in vitro* HCT-116 cell going, through time of intracellular ROS and apoptosis or necrobiosis selection. It similarly caused down regulation of PI3K/AKT/mTOR sdt pathway and moreover its subsequent downstream p70S6K and E4-BP1 proteins. Simultaneously, pristimerin shows cytotoxic, apoptosis and against metastatic

effect on HCT-116 in both *in-vivo* and *in-vitro* [89].

Apigenin: Apigenin (AP) is a characteristic flavonoid which played role against metastasis in numerous kinds of malignancies including colorectal cancer [90, 91]. Literature revealed that AP suppressed pyruvate kinase M2 (PKM2) movement in HCT116 cells *in vitro*. RT-PCR and western smudge examines demonstrated that AP could make sure about a low PKM2/PKM1 proportion in HCT116 cells by obstructing the β -catenin/c-Myc/PTBP1 signal pathway. Henceforth, PKM2 goes about as a novel potential objective of AP against colon malignant growth [92].

Quercetin: Quercetin, a natural flavanol, present in many commonly consumed food items, widely exhibited the inhibitory effect on colorectal cancer through different mechanisms such as cell cycle arrest, apoptosis, modulation of estrogen receptors, antioxidant replication, regulation of signaling pathways, inhibition or suppression of metastasis and angiogenesis [93, 94]. The effect of quercetin on cell viability was determined by MTT and colony formation assays, and apoptosis was determined by using flow cytometry by marking cells with Annexin V-FITC. KRAS-mutant cells were more responsive to quercetin-induced apoptosis than wild-type cells. The

activation of caspase was involved in quercetin-induced apoptosis. Quercetin activated JNK pathway in KRAS-mutant cells. The results of the present study suggested that the treatment with quercetin is potentially a useful for the treatment of CRCs carrying KRAS mutations [94]. Quercetin also upgraded 5-fluorouracil-incited apoptosis in MSI colorectal malignant cells through p53 adjustment [95].

CONCLUSION

Colorectal cancer is one of the leading causes of death worldwide. Among all cancers, CRC is considered as the second most common cause of death in developed and undeveloped countries. Many researches are going on for improving the treatment of CRC. Phytochemicals like curcumin, quercetin, apigenin, pristimerin, resveratrol, scutellarin etc are effective in CRC. Sometimes these agents are used in combination with other molecules for better results. According to the literature, among these molecules curcumin and resveratrol which are in the clinical trials may come in the market as lead molecules for the treatment of CRC.

REFERENCES

- [1] Mondal A, Bose S, Banerjee S, Patra JK, Malik J, Mandal SK, Kilpatrick KL, Das G, Kerry RG, Fimognari C, Bishayee A. Marine Cyanobacteria and Microalgae Metabolites—A Rich Source of Potential Anticancer Drugs. *Marine Drugs*. 18(9); 2020, 476.
- [2] Roy A, Mandal SK, Ramadan MA. Prevention and Treatment of Cancer with Alternative Anticancer Approach: Current Scenario. *Egyptian Journal of Chemistry*. 63(9); 2020, 3229-45.
- [3] Mandal SK, Debnath U, Kumar A, Thomas S, Mandal SC, Choudhury MD, Palit P. Natural Sesquiterpene Lactones in the Prevention and Treatment of Inflammatory Disorders and cancer: A Systematic Study of this Emerging Therapeutic Approach based on Chemical and Pharmacological Aspect. *Letters in Drug Design & Discovery*. 17(9); 2020, 1102-16.
- [4] Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut*. 66(4); 2017, 683-91.
- [5] Markowitz SD, Bertagnolli MM. Molecular basis of colorectal cancer. *New England Journal of Medicine*. 361(25); 2009, 2449-60.
- [6] Kheirleaid, E.A., Miller, N. and Kerin, M.J. Molecular biology of colorectal cancer: Review of the literature. *American Journal of Molecular Biology*. 03(02); 2013, 72-80.
- [7] Aggarwal B, Prasad S, Sung B, Krishnan S, Guha S. Prevention and treatment of colorectal cancer by natural agents from mother nature. *Current colorectal cancer reports*. 9(1); 2013, 37-56.

- [8] Johnson CM, Wei C, Ensor JE, Smolenski DJ, Amos CI, Levin B, Berry DA. Meta-analyses of colorectal cancer risk factors. *Cancer causes & control*. 24(6); 2013, 1207-22.
- [9] Benarba B, Pandiella A. Colorectal cancer and medicinal plants: Principle findings from recent studies. *Biomedicine & Pharmacotherapy*. 107; 2018, 408-23.
- [10] Datta R, Bose S, Mandal SK. Evaluation of In vitro Hepatic Toxicity of leaves of *Pterospermum acerifolium* (L.) Willd. Evaluation. *Asian Journal of Pharmaceutical and Clinical Research*. 13(5); 2020, 118-120.
- [11] Mandal SK, Pal H, Pal I, Bose S. Biological Potential of *Elephantopus scaber* Linn. *International Journal of Pharmaceutical Sciences*. 50(2); 2018, 130-4.
- [12] Banerjee S, Bose S, Mandal SC, Dawn S, Sahoo U, A Ramadan M, Mandal SK. Pharmacological Property of Pentacyclic Triterpenoids. *Egyptian Journal of Chemistry*. 62(Special Issue (Part 1) Innovation in Chemistry); 2019, 13-35.
- [13] Mandal SK, Das A, Dey S, Sahoo U, Bose S, Bose A, Dhiman N, Madan S, Ramadan MA. Bioactivities of Allicin and Related Organosulfur Compounds from Garlic: Overview of the Literature since 2010. *Egyptian Journal of Chemistry*. 62(Special Issue (Part 1) Innovation in Chemistry); 2019, 1-11.
- [14] de Souza Tavares W, Akhtar Y, Gonçalves GL, Zanuncio JC, Isman MB. Turmeric powder and its derivatives from *Curcuma longa* rhizomes: insecticidal effects on cabbage looper and the role of synergists. *Scientific reports*. 6; 2016, 34093.
- [15] Shishodia S, Chaturvedi MM, Aggarwal BB. Role of curcumin in cancer therapy. *Current problems in cancer*. 31(4); 2007, 243-305.
- [16] Li YH, Niu YB, Sun Y, Zhang F, Liu CX, Fan L, Mei QB. Role of phytochemicals in colorectal cancer prevention. *World journal of gastroenterology: WJG*. 21(31); 2015, 9262.
- [17] Shehzad A, Wahid F, Lee YS. Curcumin in cancer chemoprevention: molecular targets, pharmacokinetics, bioavailability, and clinical trials. *Archiv der Pharmazie*. 343(9); 2010, 489-99.
- [18] Dimas K, Tsimplouli C, Houchen C, Pantazis P, Sakellaridis N, Tsangaris GT, Ramanujam RP. An ethanol extract of Hawaiian turmeric: extensive in vitro anticancer activity against human colon cancer cells. *Altern. Ther*. 21; 2015, 46-54.
- [19] Jayaprakasha GK, Murthy KN, Patil BS. Enhanced colon cancer chemoprevention of curcumin by nanoencapsulation with whey protein. *European journal of pharmacology*. 789; 2016, 291-300.
- [20] Dasiram JD, Ganesan R, Kannan J, Kotteeswaran V, Sivalingam N. Curcumin inhibits growth potential by G1 cell cycle arrest and induces apoptosis in p53-mutated COLO 320DM human colon adenocarcinoma cells. *Biomedicine & Pharmacotherapy*. 86; 2017, 373-80.

- [21] Sakuma S, Maruyama C, Kohda T, Fujimoto Y. Curcumin inhibits the proliferation of a human colorectal cancer cell line Caco-2 partially by both apoptosis and G2/M cell cycle arrest. *International journal of pharmacology research*. 4; 2014, 84-90.
- [22] Wang CZ, Yuan CS. Potential role of ginseng in the treatment of colorectal cancer. *The American journal of Chinese medicine*. 36(6); 2008, 1019-28.
- [23] Jin Y, Hofseth AB, Cui X, Windust AJ, Poudyal D, Chumanevich AA, Matesic LE, Singh NP, Nagarkatti M, Nagarkatti PS, Hofseth LJ. American ginseng suppresses colitis through p53-mediated apoptosis of inflammatory cells. *Cancer Prevention Research*. 3(3); 2010, 339-47.
- [24] Vayghan HJ, Ghadimi SS, Nourazarian AR. Preventive and therapeutic roles of ginseng-focus on colon cancer. *Asian Pacific Journal of Cancer Prevention*. 15(2); 2014, 585-8.
- [25] Qi LW, Wang CZ, Yuan CS. American ginseng: potential structure–function relationship in cancer chemoprevention. *Biochemical pharmacology*. 80(7); 2010, 947-54.
- [26] Park JW, Lee JC, Ann S, Seo DW, Choi WS, Yoo YH, Park SK, Choi JY, Sung Hee Um SH, Han JW. A fermented ginseng extract, BST204, inhibits proliferation and motility of human colon cancer cells. *The Korean Society of Applied Pharmacology*. 19(2); 2011, 211-7.
- [27] Ji X, Avula B, Khan IA. Quantitative and qualitative determination of six xanthenes in *Garcinia mangostana* L. by LC–PDA and LC–ESI-MS. *Journal of pharmaceutical and biomedical analysis*. 43(4); 2007, 1270-6.
- [28] Sun J, Chu YF, Wu X, Liu RH. Antioxidant and antiproliferative activities of common fruits. *Journal of agricultural and food chemistry*. 50(25); 2002, 7449-54.
- [29] Yoo JH, Kang K, Jho EH, Chin YW, Kim J, Nho CW. α - and γ -Mangostin inhibit the proliferation of colon cancer cells via β -catenin gene regulation in Wnt/cGMP signalling. *Food Chemistry*. 129(4); 2011, 1559-66.
- [30] Aisha AF, Abu-Salah KM, Ismail Z, Majid AM. In vitro and in vivo anti-colon cancer effects of *Garcinia mangostana* xanthenes extract. *BMC complementary and alternative medicine*. 12(1); 2012, 104.
- [31] Chang HF, Yang LL. Gamma-mangostin, a micronutrient of mangosteen fruit, induces apoptosis in human colon cancer cells. *Molecules*. 17(7); 2012, 8010-21.
- [32] Akao Y, Nakagawa Y, Nozawa Y. Anti-cancer effects of xanthenes from pericarps of mangosteen. *International Journal of Molecular Sciences*. 9(3); 2008, 355-70.
- [33] Muko KN, Ohiri FC. A preliminary study on the anti-inflammatory properties of *Emilia sonchifolia* leaf extracts. *Fitoterapia*. 71(1); 2000, 65-8.
- [34] Shylesh BS, Padikkala J. Antioxidant and anti-inflammatory activity of *Emilia*

- sonchifolia. *Fitoterapia*. 70(3); 1999, 275-8.
- [35] Shylesh BS, Padikkala J. In vitro cytotoxic and antitumor property of *Emilia sonchifolia* (L.) DC in mice. *Journal of Ethnopharmacology*. 73(3); 2000, 495-500.
- [36] Lan YH, Wu YC, Wu KW, Chung JG, Lu CC, Chen YL, Wu TS, Yang JS. Death receptor 5-mediated TNFR family signaling pathways modulate γ -humulene-induced apoptosis in human colorectal cancer HT29 cells. *Oncology reports*. 25(2); 2011, 419-24.
- [37] Lan YH, Chiang JH, Huang WW, Lu CC, Chung JG, Wu TS, Jhan JH, Lin KL, Pai SJ, Chiu YJ, Tsuzuki M. Activations of both extrinsic and intrinsic pathways in HCT 116 human colorectal cancer cells contribute to apoptosis through p53-mediated ATM/Fas signaling by *Emilia sonchifolia* extract, a folklore medicinal plant. *Evidence-Based Complementary and Alternative Medicine*. 2012 Oct; 2012.
- [38] Bai N, He K, Zhou Z, Lai CS, Zhang L, Quan Z, Shao X, Pan MH, Ho CT. Flavonoids from *Rabdosia rubescens* exert anti-inflammatory and growth inhibitory effect against human leukemia HL-60 cells. *Food Chemistry*. 122(3); 2010, 831-5.
- [39] Guo S, Cui X, Jiang M, Bai L, Tian X, Guo T, Liu Q, Zhang L, Ho CT, Bai N. Simultaneous characterization and quantification of 17 main compounds in *Rabdosia rubescens* by high performance liquid chromatography. *Journal of food and drug analysis*. 25(2); 2017, 417-24.
- [40] Jie Yang a, Hai Jiang , Chunyu Wang, Bo Yang , Lijun Zhao , Dongling Hua, Guihua Qiu , Xiaolin Dong , Bin Xiao, Oridonin triggers apoptosis in colorectal carcinoma cells and suppression of microRNA-32 expression augments oridonin-mediated apoptotic effects. *Biomedicine & Pharmacotherapy*. 72; (2015), 125–134.
- [41] Gao FH, Hu XH, Li W, Liu H, Zhang YJ, Guo ZY, Xu MH, Wang ST, Jiang B, Liu F, Zhao YZ. Oridonin induces apoptosis and senescence in colorectal cancer cells by increasing histone hyperacetylation and regulation of p16, p21, p27 and c-myc. *BMC cancer*. 10(1); 2010, 610.
- [42] Hannachi H, Elfalleh W, Marzouk S. Oil, protein, antioxidants and free radical scavenging activity of stone from wild olive trees (*Olea europaea* L.). *Pakistan Journal of Pharmaceutical Sciences*. 26; 2013, 503-10.
- [43] Fuentes E, Paucar F, Tapia F, Ortiz J, Jimenez P, Romero N. Effect of the composition of extra virgin olive oils on the differentiation and antioxidant capacities of twelve monovarietals. *Food chemistry*. 243; 2018, 285-94.
- [44] Cebe GE, Konyalıoğlu S, Zeybek U. Antioxidant activity of *Olea europaea* var. *europaea* leaves infusion. *Ege Üniversitesi Ziraat Fakültesi Dergisi*. 49(3); 2012, 209-12.
- [45] Lucas L, Russell A, Keast R. Molecular mechanisms of inflammation. *Anti-*

- inflammatory benefits of virgin olive oil and the phenolic compound oleocanthal. *Current pharmaceutical design*. 17(8); 2011, 754-68.
- [46] Makowska-Wąs J, Galanty A, Gdula-Argasińska J, Tyszka-Czochara M, Szewczyk A, Nunes R, Carvalho IS, Michalik M, Paśko P. Identification of predominant phytochemical compounds and cytotoxic activity of wild olive leaves (*Olea europaea* L. ssp. *sylvestris*) harvested in south Portugal. *Chemistry & biodiversity*. 14(3); 2017, e1600331.
- [47] Zeriouh W, Nani A, Belarbi M, Dumont A, de Rosny C, Aboura I, Ghanemi FZ, Murtaza B, Patoli D, Thomas C, Apetoh L. Phenolic extract from oleaster (*Olea europaea* var. *Sylvestris*) leaves reduces colon cancer growth and induces caspase-dependent apoptosis in colon cancer cells via the mitochondrial apoptotic pathway. *PloS one*. 12(2); 2017, e0170823.
- [48] Shamshoum H, Vlavcheski F, Tsiani E. Anticancer effects of oleuropein. *Biofactors*. 43(4); 2017, 517-28.
- [49] Lee SY, Choi SU, Lee KR. Three new megastigmane glycosides from *Hylomecon vernalis*. *Bull. Korean Chemical Society*. 32; 2011, 3813-6.
- [50] Lee SY, Kim KH, Lee IK, Lee KH, Choi SU, Lee KR. A new flavonol glycoside from *Hylomecon vernalis*. *Archives of Pharmacal Research*. 35(3); 2012, 415-21.
- [51] Sun J, Zhang X, Sun Y, Tang ZS, Guo DY. Effects of *Hylomecon vernalis* ethanol extracts on cell cycle and apoptosis of colon cancer cells. *Molecular Medicine Reports*. 15(6); 2017, 3485-92.
- [52] Xu LN, Lu BN, Hu MM, Xu YW, Han X, Qi Y, Peng JY. Mechanisms involved in the cytotoxic effects of berberine on human colon cancer HCT-8 cells. *Biocell*. 36(3); 2012, 113-20.
- [53] Mandal SK, Maji AK, Mishra SK, Ishfaq PM, Devkota HP, Silva AS, Das N. Goldenseal (*Hydrastis canadensis* L.) and its active constituents: a critical review of their efficacy and toxicological issues. *Pharmacological Research*. 160; 2020, 105085.
- [54] La X, Zhang L, Li Z, Yang P, Wang Y. Berberine-induced autophagic cell death by elevating GRP78 levels in cancer cells. *Oncotarget*. 8(13); 2017, 20909.
- [55] Eshun K, He Q. Aloe Vera: a valuable ingredient for the food, pharmaceutical and cosmetic industries—a review. *Critical reviews in food science and nutrition*. 44(2); 2004, 91-6.
- [56] Foster M, Hunter D, Samman S. Evaluation of the nutritional and metabolic effects of Aloe vera. Chapter; 2011.
- [57] Radha MH, Laxmipriya NP. Evaluation of biological properties and clinical effectiveness of Aloe vera: A systematic review. *Journal of traditional and complementary medicine*. 5(1); 2015, 21-6.
- [58] Manvitha K, Bidya B. Aloe vera: a wonder plant its history, cultivation and medicinal uses. *Journal of Pharmacognosy and Phytochemistry*. 2(5); 2014, 85-8.

- [59] Sánchez-Machado DI, López-Cervantes J, Sendón R, Sanches-Silva A. Aloe vera: Ancient knowledge with new frontiers. *Trends in Food Science & Technology*. 61; 2017, 94-102.
- [60] Frolidi G, Baronchelli F, Marin E, Grison M. Antiglycation activity and HT-29 cellular uptake of aloe-Emodin, aloin, and aloe arborescens leaf extracts. *Molecules*. 24(11); 2019, 2128.
- [61] Pooja T, Karunagaran D. Emodin suppresses Wnt signaling in human colorectal cancer cells SW480 and SW620. *European journal of pharmacology*. 742; 2014, 55-64.
- [62] Yang N, Zhao Y, Wang Z, Liu Y, Zhang Y. Scutellarin suppresses growth and causes apoptosis of human colorectal cancer cells by regulating the p53 pathway. *Molecular medicine reports*. 15(2); 2017, 929-35.
- [63] EghbaliFeriz S, Taleghani A, Tayarani-Najaran Z. Scutellaria: Debates on the anticancer property. *Biomedicine & Pharmacotherapy*. 105; 2018, 1299-310.
- [64] Zhu PT, Mao M, Liu ZG, Tao L, Yan BC. Scutellarin suppresses human colorectal cancer metastasis and angiogenesis by targeting ephrin2. *American Journal of Translational Research*. 9(11); 2017, 5094.
- [65] Li H, Huang D, Gao Z, Lv Y, Zhang L, Cui H, Zheng J. Scutellarin inhibits cell migration by regulating production of $\alpha\beta6$ integrin and E-cadherin in human tongue cancer cells. *Oncology reports*. 24(5); 2010, 1153-60.
- [66] Chan JY, Tan BK and Lee SC: Scutellarin sensitizes drug-evoked colon cancer cell apoptosis through enhanced caspase-6 activation. *Anticancer Research*. 29; 2009, 3043–3047.
- [67] Subramaniam S, Selvaduray KR, Radhakrishnan AK. Bioactive compounds: natural defense against cancer. *Biomolecules*. 9(12); 2019, 758.
- [68] Lu J, Papp LV, Fang J, Rodriguez-Nieto S, Zhivotovsky B, Holmgren A. Inhibition of mammalian thioredoxin reductase by some flavonoids: implications for myricetin and quercetin anticancer activity. *Cancer research*. 66(8); 2006, 4410-8.
- [69] Yao Y, Lin G, Xie Y, Ma P, Li G, Meng Q, Wu T. Preformulation studies of myricetin: a natural antioxidant flavonoid. *Die Pharmazie-An International Journal of Pharmaceutical Sciences*. 69(1); 2014, 19-26.
- [70] Kim ME, Ha TK, Yoon JH, Lee JS. Myricetin induces cell death of human colon cancer cells via BAX/BCL2-dependent pathway. *Anticancer research*. 34(2); 2014, 701-6.
- [71] Subramaniam S, Selvaduray KR, Radhakrishnan AK. Bioactive compounds: natural defense against cancer. *Biomolecules*. 9(12); 2019, 758.
- [72] Ren Z, Zou W, Cui J, Liu L, Qing Y, Li Y. Geraniin suppresses tumor cell growth and triggers apoptosis in human glioma via inhibition of STAT3 signaling. *Cytotechnology*. 69(5); 2017, 765-73.

- [73] Guo X, Dai X, Ni J, Ma X, Xue J, Wang X. Geraniin differentially modulates chromosome stability of colon cancer and noncancerous cells by oppositely regulating their spindle assembly checkpoint. *Environmental and molecular mutagenesis*. 60(3); 2019, 254-68.
- [74] Guo X, Wang H, Ni J, Liang Z, Wu X, Xue J, Wang X. Geraniin selectively promotes cytostasis and apoptosis in human colorectal cancer cells by inducing catastrophic chromosomal instability. *Mutagenesis*. 33(4); 2018, 271-81.
- [75] Subramaniam S, Selvaduray KR, Radhakrishnan AK. Bioactive compounds: natural defense against cancer. *Biomolecules*. 9(12); 2019, 758.
- [76] Aggarwal BB, Sundaram C, Prasad S, Kannappan R. Tocotrienols, the vitamin E of the 21st century: it's potential against cancer and other chronic diseases. *Biochemical pharmacology*. 80(11); 2010, 1613-31.
- [77] Zhang JS, Zhang SJ, Li Q, Liu YH, He N, Zhang J, Zhou PH, Li M, Guan T, Liu JR. Tocotrienol-rich fraction (TRF) suppresses the growth of human colon cancer xenografts in Balb/C nude mice by the Wnt pathway. *PLoS One*. 10(3); 2015, e0122175.
- [78] Li Y, Sun Y, Fan L, Zhang F, Meng J, Han J, Guo X, Zhang D, Zhang R, Yue Z, Mei Q. Paris saponin VII inhibits growth of colorectal cancer cells through Ras signaling pathway. *Biochemical pharmacology*. 88(2); 2014, 150-7.
- [79] Fan L, Li Y, Sun Y, Yue Z, Meng J, Zhang X, Zhang R, Zhang D, Zhang F, Mei Q. Paris saponin VII inhibits metastasis by modulating matrix metalloproteinases in colorectal cancer cells. *Molecular medicine reports*. 11(1); 2015, 705-11.
- [80] Qin J, Chen JX, Zhu Z, Teng JA. Genistein inhibits human colorectal cancer growth and suppresses miR-95, Akt and SGK1. *Cellular physiology and biochemistry*. 35(5); 2015, 2069-77.
- [81] Qin J, Teng J, Zhu Z, Chen J, Huang WJ. Genistein induces activation of the mitochondrial apoptosis pathway by inhibiting phosphorylation of Akt in colorectal cancer cells. *Pharmaceutical biology*. 54(1); 2016, 74-9.
- [82] Yu S, Ye X, Chen L, Xie X, Zhou Q, Lian XY, Zhang Z. Cytotoxic and anti-colorectal tumor effects of sulfated saponins from sea cucumber *Holothuria moebii*. *Phytomedicine*. 22(12); 2015, 1112-9.
- [83] Juan ME, Alfaras I, Planas JM. Colorectal cancer chemoprevention by trans-resveratrol. *Pharmacological Research*. 65(6); 2012, 584-91.
- [84] Ji Q, Liu X, Fu X, Zhang L, Sui H, Zhou L, Sun J, Cai J, Qin J, Ren J, Li Q. Resveratrol inhibits invasion and metastasis of colorectal cancer cells via MALAT1 mediated Wnt/ β -catenin signal pathway. *PloS one*. 8(11); 2013, e78700.
- [85] Li D, Wang G, Jin G, Yao K, Zhao Z, Bie L, Guo Y, Li N, Deng W, Chen X, Chen

- B. Resveratrol suppresses colon cancer growth by targeting the AKT/STAT3 signaling pathway. *International journal of molecular medicine*. 43(1); 2019, 630-40.
- [86] Li YH, Niu YB, Sun Y, Zhang F, Liu CX, Fan L, Mei QB. Role of phytochemicals in colorectal cancer prevention. *World journal of gastroenterology: WJG*. 21(31); 2015, 9262.
- [87] Ahmed K, Zaidi SF, Cui ZG, Zhou D, Saeed SA, Inadera H. Potential proapoptotic phytochemical agents for the treatment and prevention of colorectal cancer. *Oncology Letters*. 18(1); 2019, 487-98.
- [88] Yousef BA, Guerram M, Hassan HM, Hamdi AM, Zhang LY, Jiang ZZ. Pristimerin demonstrates anticancer potential in colorectal cancer cells by inducing G1 phase arrest and apoptosis and suppressing various pro-survival signaling proteins. *Oncology reports*. 35(2); 2016, 1091-100.
- [89] Yousef BA, Hassan HM, Guerram M, Hamdi AM, Wang B, Zhang LY, Jiang ZZ. Pristimerin inhibits proliferation, migration and invasion, and induces apoptosis in HCT-116 colorectal cancer cells. *Biomedicine & Pharmacotherapy*. 79; 2016, 112-9.
- [90] Madunić J, Madunić IV, Gajski G, Popić J, Garaj-Vrhovac V. Apigenin: A dietary flavonoid with diverse anticancer properties. *Cancer letters*. 413; 2018, 11-22.
- [91] Kashyap D, Sharma A, Tuli HS, Sak K, Garg VK, Buttar HS, Setzer WN, Sethi G. Apigenin: A natural bioactive flavone-type molecule with promising therapeutic function. *Journal of Functional Foods*. 48; 2018, 457-71.
- [92] Dai J, Van Wie PG, Fai LY, Kim D, Wang L, Poyil P, Luo J, Zhang Z. Down regulation of NEDD9 by apigenin suppresses migration, invasion, and metastasis of colorectal cancer cells. *Toxicology and applied pharmacology*. 311; 2016, 106-12.
- [93] Darband SG, Kaviani M, Yousefi B, Sadighparvar S, Pakdel FG, Attari JA, Mohebbi I, Naderi S, Majidinia M. Quercetin: A functional dietary flavonoid with potential chemo-preventive properties in colorectal cancer. *Journal of cellular physiology*. 233(9); 2018, 6544-60.
- [94] Yang Y, Wang T, Chen D, Ma Q, Zheng Y, Liao S, Wang Y, Zhang J. Quercetin preferentially induces apoptosis in KRAS-mutant colorectal cancer cells via JNK signaling pathways. *Cell biology international*. 43(2); 2019, 117-24.
- [95] Xavier CP, Lima CF, Rohde M, Pereira-Wilson C. Quercetin enhances 5-fluorouracil-induced apoptosis in MSI colorectal cancer cells through p53 modulation. *Cancer chemotherapy and pharmacology*. 68(6); 2011, 1449-57.