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## Review

## Regulation of micro-RNA, epigenetic factor by natural products for the treatment of cancers: Mechanistic insight and translational association

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## ABSTRACT

From onset to progression, cancer is a ailment that might take years to grow. All common epithelial malignancies, have a long latency period, frequently 20 years or more, different gene may contain uncountable mutations if they are clinically detectable. MicroRNAs (miRNAs) are around 22nt non-coding RNAs that control gene expression sequence-specifically through translational inhibition or messenger degradation of RNA (mRNA). Epigenetic processes of miRNA control genetic variants through genomic DNA methylation, post-translation histone modification, rework of the chromatin, and microRNAs. The field of miRNAs has opened a new era in understanding small non-coding RNAs since discovering their fundamental mechanisms of action. MiRNAs have been found in viruses, plants, and animals through molecular cloning and bioinformatics approaches. Phytochemicals can invert the epigenetic aberrations, a leading cause of the cancers of various organs, and act as an inhibitor of these changes. The advantage of phytochemicals is that they only function on cells that cause cancer without affecting normal cells. Phytochemicals appear to play a significant character in modulating miRNA expression, which is linked to variations in oncogenes, tumor suppressors, and cancer-derived protein production, according to several studies. In addition to standard anti-oxidant or anti-inflammatory properties, the initial epigenetic changes associated with cancer prevention may be modulated by many polyphenols. In correlation with miRNA and epigenetic factors to treat cancer some of the phytochemicals, including polyphenols, curcumin, resveratrol, indole-3-carbinol are studied in this article.

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## 1. Introduction

Despite advances in medicine, cancer is now the world's leading death cause. Now need a more safe and effective strategy for cancer prevention. Treatment through dietary phytochemicals is preferable due to its safety, easy access, and less toxicity (Pratheeshkumar, Son, Korangath, Manu, & Siveen, 2015). Many epidemiological studies and research based on diet intervention in human beings using experimental animals have provided us much evidence to recommend the progression of the huge variety of neoplasms due to the lifestyle of humans and many environmental factors. The etiology of human cancer is focused on organic carcinogens, toxins in the atmosphere, physical carcinogens, and dietary impurity (LISOUSA, 2021).

On the other hand, some lifestyle factors can also enhance the progression and development of cancer like smoking, enhanced consumption of fat, exposure to sunlight, consumption of an increased amount of alcohol, and chronic stress. It has also been proposed that mother-nutrition imbalances or metabolic abnormalities during embryo development adversely affect the health of offspring and may be inherited. The adverse effect of genetic and epigenetic events may consider as Carcinogenic (Shankar, Kumar, & Srivastava, 2013).

Micro RNAs are minor, non-coding RNAs and almost 20–24 nucleotides involved in genetic material and cell signaling regulation. About 2469 miRNAs are detected in an individual, and many researchers have considered that miRNA dysregulation performs a substantial part in the growth of cancer (Acunzo, Romano, Wernicke, & Croce, 2015). Many plant chemicals can regulate the manifestation of many non-coding RNAs, which are cancer-associated (Debnath, Nath, Kim, & Lee, 2017). Currently, the expression of non-coding RNAs has conclusively related to cancer growth, and the profile of miRNA can be applied to categorize human cancers (Jansson & Lund, 2012). RNA polymerase II miRNAs are generally transcribed and encoded in our genome (Chuang & Jones, 2007). The role of human microRNAs within various kinds of cancer can be described by their transcriptional targets and level of expression in that way up-regulated micro RNAs are under oncogenic classification in comparison to down-regulated undergo classification of tumor suppressors (Hargraves, He, & Firestone, 2016).

The carcinogenic side effects are hereditary and epigenetic. Linear changes are created in epigenetics, but not in gene expression due to fluctuations in the DNA structure. In cell life, epigenetic mechanisms have always existed. This comprises DNA methylation, microRNA expression, histone modifications, chromatin remodeling, and multi-gene expression non-coding RNA silencing. Many studies revealed that epigenetic events are the leading cause of cancer (S. Sharma, Kelly, & Jones, 2010) and involve the inactivation of retrotransposons through genomic instability (Kanwal & Gupta, 2010; Shukla, Meeran, & Katiyar, 2014). The vital epigenetic processes for gene expression regulation are methylation of DNA, chromatin alteration by histone and non-histone proteins post-translational modifications, and micro RNA (non-coding RNA), which can degrade messenger RNA, or their process of translation undergo modulation. In regulating the proper functioning of cells at all stages, these epigenetic changes include development and differentiation. However, modification in targets of epigenetic events may also lead to many life-threatening diseases, including cancer (Thakur, Deb, Babcook, & Gupta, 2014). miRNAs correlated with epigenetic events that might also show a substantial part in the control of methylation of DNA and histone modifications (Chuang & Jones, 2007; Schröder et al., 2021; Sun et al., 2021).

There are a wide range of methods of treating cancer, including chemotherapy and synthetic medicines. Plant extract for disease treatment is as early as civilization and traditional medicines before forming an enormous part of the routine treatment of various diseases (Gavamukulya, Abou-Elella, Wamunyokoli, & AEI-Shemy, 2014). Rendering to the suggestion of the world health organization (WHO), almost all developed countries are moving back toward the conventional medicinal system. Approximately 65% of the world's overall population has integrated the value of herbs used as an herbal medicine for health care. It is estimated that almost 25% of total drugs authorized nowadays are derived from plants (Mukhopadhyay, Banerjee, & Nath, 2012).

Plant extracted chemicals have various valuable properties, and they can use against inflammation and have anti-cancerous properties (Gavamukulya et al., 2014). The source of these phytochemicals are vegetables, herbs, fruits, many dietary supplements, and beverages. Therefore, consuming food that is rich in vegetables and fruit can minimize the cancer risk. Almost 47% of drugs against cancer are plant-based, which is affiliated with the FDA (Debnath

et al., 2017). Nearby not before a decade, researches show that plant extracted chemicals could target the functioning of many epigenetic events, like DNMTs and HDACs it might be effective to stop and remedy many ailments involving cancer (Mortoglou, Tabin, Arisan, Kocher, & Uysal-Onganer, 2021; Watson, Beaver, Williams, Dashwood, & Ho, 2013). In correlation with miRNA and epigenetic factors to treat cancer some of the phytochemicals including tea polyphenols, curcumin, resveratrol, indole-3-carbinol (Shukla et al., 2014).

## 2. Effect of epigenetic events in cancer development

Epigenetics means analyzing a set of reversible but inherited cell or genetic modifications deprived of any modifications in the DNA sequence (Henikoff & Matzke, 1997). Thanks to its reversible nature and early detection, epigenetic changes have been focused on critical drug targets for cancer prevention (Saetrom, Snøve, & Rossi, 2007). Alteration of epigenetic events leads to various diseases like cancer (Ellis, Atadja, & Johnstone, 2009).

Methylation in the mammalian genome takes place at cytosine base near 5' guanine base in CpG dinucleotide. CpG nucleotides are in a 0.5 to 4 kb genome region known as CpG rich region (Takai & Jones, 2002). Hypermethylation of these promoter regions in cancer and unsuitable transcriptional gene silencing occurs to see the epigenetic event's effect first to see how this methylation occurs and then affect cancer development (Fig. 1). The epigenetic change can be observed in almost all forms of human neoplasms (Price & Spackman, 2000). The DNMT1 enzyme preserves DNA replication methylation in mammalian cells, while previously unmethylated DNMT3a and 3b methylate may perform an important part in cancer genesis (Issa & Kantarjian, 2009). Sequences in DNA, rich in CG repeats, called islands of chromosomal chromosomes, occur, and these repeated sequences are heavily methylated (Kopelovich, Crowell, & Fay, 2003). CpG is typically unmethylated within the promoter regions of a gene. Raised level of methylation of CpG in the promoters of genes might move toward tumor suppressor transcriptional silencing (Sun et al., 2021; Zheng et al., 2021).

In similarity, global DNA hypomethylation on the CpG islands could generate the frequently observed genomic instability in malignant cells (Goelz, Vogelstein, & Feinberg, 1985). The DNA of cancer cells is known to have changed methylation patterns. There have been two patterns: vast areas of global genome hypomethylation and localized areas of hypermethylation within gene promoter regions at some particular sites, CpG islands (Goel, Un Nisa, Reza, Rahman, & Aamer, 2019; Mehta et al., 2006).

Researchers constantly struggled to establish a definite role to ensure successive stimulation of protooncogenes & hypomethylation. A clear illustration of this link was present in the gene BCL-2 and the chronic B-cell human while hypomethylation was not sufficiently proved and protooncogenes were activated. Although reduced methylation levels for genes like C-MYC have also been recognized in humans, it is clear that this is primarily responsible for an increased gene expression instead of just a secondary function detected in cancer cells (Sharrard, Royds, Rogers, & Shorthouse, 1992).

In a subset of human malignancies (often colorectal) with microsatellite instability, hypermethylation of the CpG zone of the promoter of the MLH1 mismatch mending gene was discovered. It is observed that microsatellite sequences are polymorphic, small, repetitive fragments of DNA among 1 and 4 simple DNA pairs dispersed along the genome, and configuration modifications are common if the cells are insufficient to repair DNA defects. The methylation of MLH1 leads to a loss of functional protection (Bhalerao et al., 2021). It impairs the cell's ability to repair mismatch occurring in the genome during replication, leading to a hundred times higher mutation rate than that found in normal cells. Around 13% of all cases of colorectal cancer sporadically have microsatellite instability and almost all of those of colorectal cancer who are inherited non-polyposis have hMLH1 and hMSH2 abnormal repair mutations. This results in microsatellite instability (Thomas, Umar, & Kunkel, 1996). In large part of microsatellite tumors, there might not be any mutational abnormality, but the expression of the protein hMLH1 is hypermethylated and lost. The pharmacologic bypass of methylation occurrences with this (5-aza-dC) also restore equally the hMLH1 protein expression, and the absence of a match repair potential is seen in colorectal

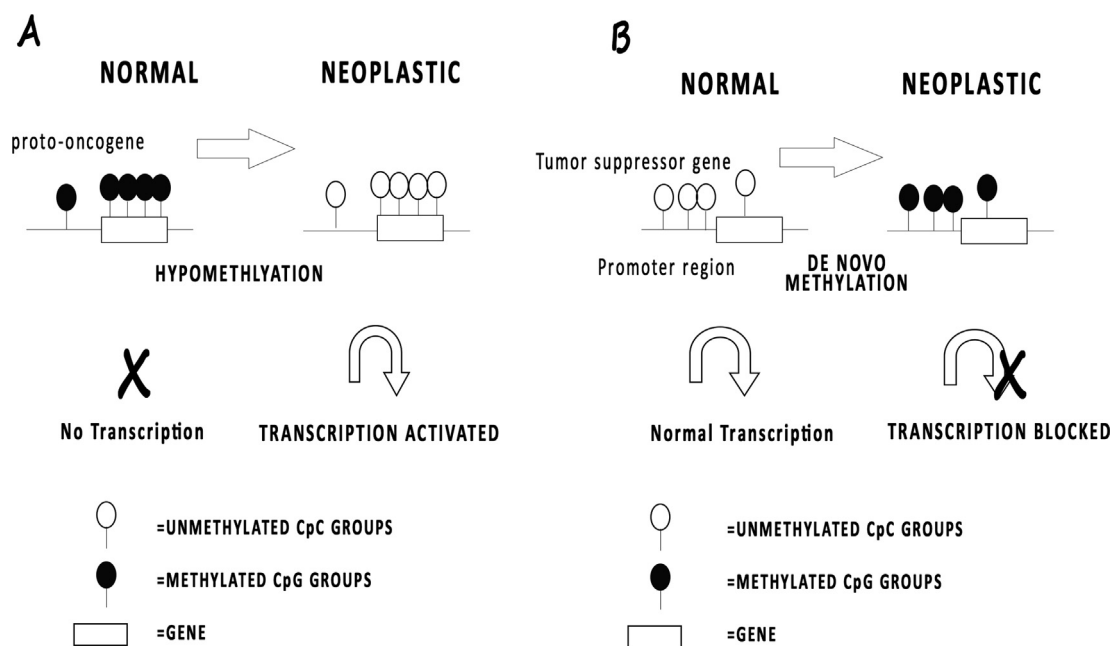


Fig. 1. Hypomethylation and transcription activation with de-novo methylation and blockage of transcription.

cancer cell lines (Herman et al., 1998). Methylation may serve as an epigenetic device to remove one genetic copy. The genetic expression can be eliminated, and functional proteins cannot be produced to enable carcinogenesis and the second genetic event or a different genetic event. The blend of events, epigenetic, and genetic in cancer is the way that inactivates all allelic sites (Fig. 2).

### 3. Role of miRNA in the development of cancer

The human genome contains around 2000 miRNAs, and these short non-coding RNAs can influence protein-coding gene expression (Fig. 3). Primary transcript cleavage, activation of mRNA degradation, and translational suppression are all aided by miRNA-mRNA base pairing complementarity. Researchers currently emphasize on miRNAs as possible diagnostic or prognostic markers (Corsini et al., 2012), and predict cancer therapy success (Samec et al., 2019).

A class of genes that have been concerned recently in many cancers MicroRNAs (miRNAs) (Si, Shen, Zheng, & Fan, 2019). In humans, several hundred miRNAs were identified. MicroRNAs can be effective regulators of gene expression, and altered miRNA can result in aberrant expression of gene products, which contributes to cancer biology. (Meng et al., 2007; Reddy, 2015; Samec et al., 2019). In numerous studies, the expression of miRNAs in malignant tissues tends to be lower than the corresponding non-malignant tissues (Kutay et al., 2006). Aberrant expression of certain microRNAs (miRNAs) targets a possible medication for cancer because modulation of single miRNAs appears to have reversed therapeutically unfavorable expression by targeting multiple genes in cancer cells (Yeh, Oh, Yoo, Kaur, & Lee, 2019).

In mammalian cells, MiR-21 is a widely expressed miRNA linked to up-regulating specific cancer types (Y. Feng & C. Tsao, 2016). In serious and haematological malignancies, MiR-21 is the most often upregulated miRNA (CG, 2006). Comprehensive research has demonstrated their role in tumour pathogenesis and all other stages of carcinogenesis.

1. Allowing miR-21 in cultured glioblastoma cells has miR-21 activated caspases and contributed to an increase in apoptotic cell death, demonstrating that it acts as an anti-apoptotic factor. (Chan et al., 2005).
2. The human miR-21 gene is located on the 17q23.2 t chromosomal site, near the fragile site FRA17B, which is one of the human papillomavirus (HPV) integration loci. (Thorland, Myers, Gostout, & Smith, 2003).
3. In hepatoma cells, miR-21 knockdown increased the expression of the tumour suppressor phosphatase and tensin counterpart deleted from chromosome 10 (PTEN), a direct target of miR-21. It inhibited tumour cell proliferation, migration, and invasion (Meng et al., 2007).

The miRNAs was found to have the highest similarity of let-7a, let-7f, let-7 g, miR-15b, miR-16, miR-21, miR-23a, miR-23b, miR-24, miR-26a, miR-29a, miR-103, miR-150 and miR-720 cells (Fehniger et al., 2010). Several researchers have shown that the overall survival, maturation, and lack of ability of NK-cells deficient in miRNA have decreased, demonstrating the essential role of miRNAs in innate immune function and paving the way for more comprehensive experiments to regulate NK-cell miRNA (Sullivan, Leong, & Fehniger, 2013).

A substantial number of researches have showed the vital function of miR-21 in tumor pathogenesis and all other stages of cancer (Wang et al., 2014). In breast cancer, miR-21 overexpression was expressively accompanying to progressive clinical stage, metastasis of the lymph nodes, and poor prognosis. MiR-21 expression has increased in both in-vitro and tissue lines of human breast cancer cells, with key implications in all stages of breast cancer pathogenesis. (Zhang & Ma, 2012). MiR-21 induces stubbornness during colon cancer by reducing the transforming growth factor  $\beta$  receptor 2 and promoting invasion and metastasis by suppressing PDCD4 (Yu et al., 2015). Evidence supports miR-21, which regulates a variety of downstream cancer-related factors as an oncogenic miRNA. MiR-21 can be used for different cancers as the diagnosis, prognosis, and therapeutic biomarker (Y.-H. Feng & C.-J. Tsao, 2016).

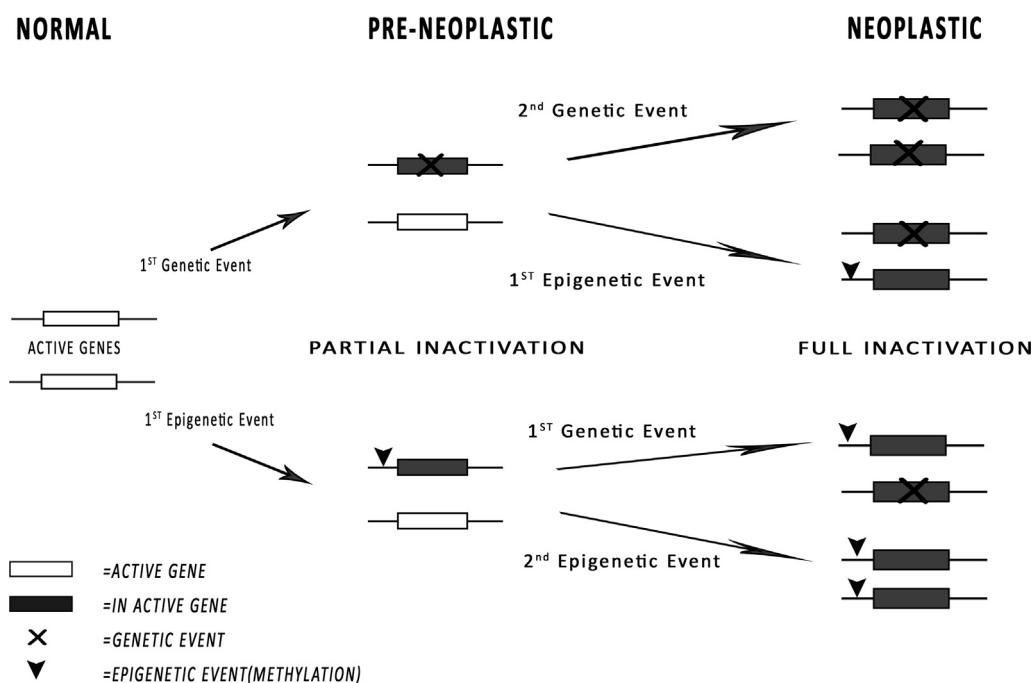


Fig. 2. Mixture of genetic and epigenetic events in cancer.

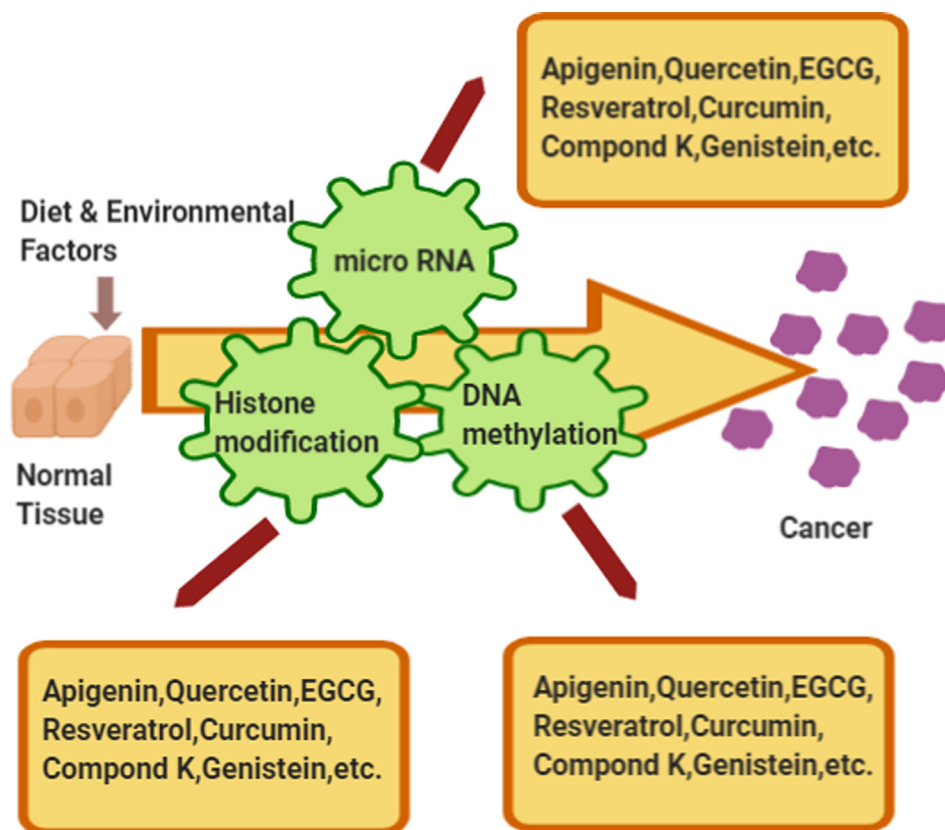


Fig. 3. Role of miRNA in the development of cancer.

#### 4. Classes and sources of phytochemicals

Phyto word derived from Greek which is meant as “**plant**” and phytochemicals are naturally existing plant-extracted compounds. Such compounds can be used to cure various illnesses, including cancer, like herbal medicine. There are several ways to treat cancer with the advancement of medicine. Still, almost all countries worldwide are going back to conventional phytochemical therapy because it is safer. These phytochemicals are bioactive molecules and are considered secondary metabolites. On the basis of chemical structure, biosynthetic origins and functioning phytochemicals are classified into sub-groups. Phytochemicals are most abundant in fruit, tea, vegetable, and chocolates (Subramanian et al., 2016).

Plant extracted chemicals have a distinctive potential to modify the level of the miRNAs across a diversity of processes, like transcriptional changes, changes in epigenetic events (without altering the nucleotide sequences alteration in the genome), and either rise or fall in the level of micro RNAs. Consequently, phytochemicals, which regulate miRNA expression in cancer, might benefit cancer treatment (Thakur et al., 2014). Nearby not before a decade, researches show that plant extracted chemicals could target the functioning of many epigenetic events; like DNMTs and HDACs it might be effective to stop and handle many diseases containing cancer (Shukla et al., 2014).

Approximately 65% of the world’s overall population has integrated the value of herbs used as an herbal medicine for health care. It is estimated that almost 25% of the total drugs authorized in the present day came from herbs (Mukhopadhyay et al., 2012). The sources of these phytochemicals are vegetables, herbs, fruits, many dietary supplements, and beverages. Consequently, the ingestion of these fruit and vegetable foods may minimize cancer risk, as shown in (Table 1) (Debnath et al., 2017).

##### 4.1. Polyphenol

###### 4.1.1. Curcumin

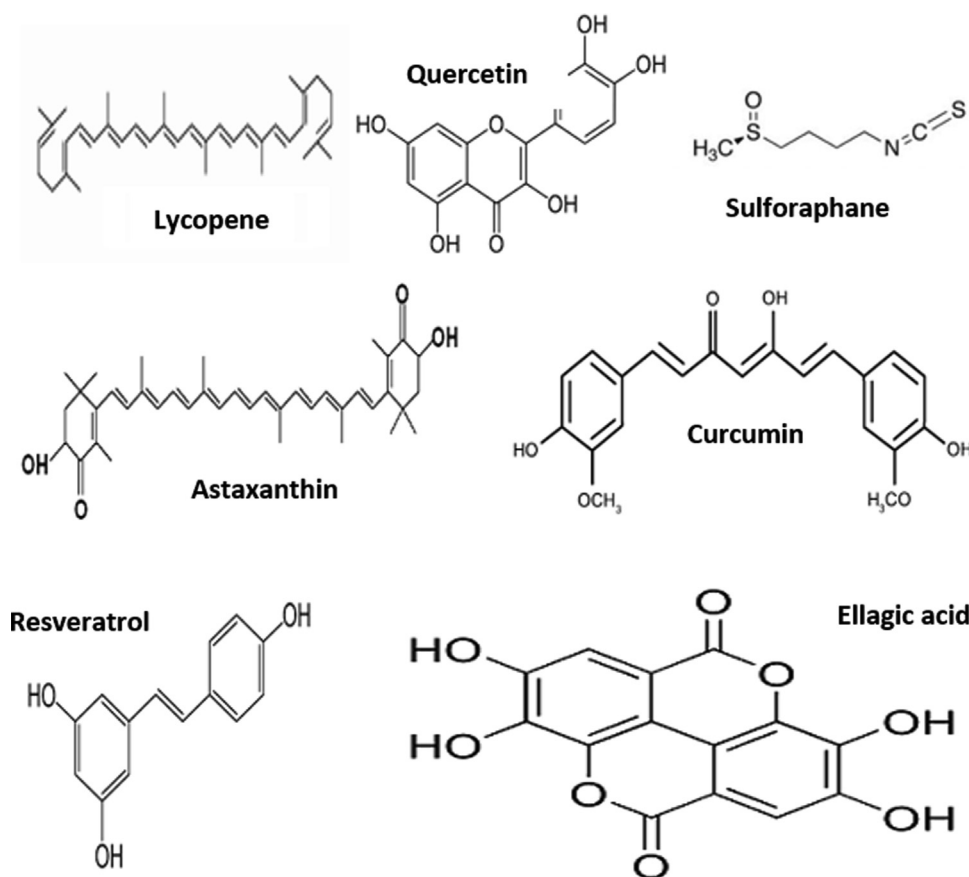
Curcumin is phytochemical, and turmeric is the source of this plant-derived compound (Shankar et al., 2013; Shukla et al., 2014). Phytochemical curcumin is a polyphenol (Fig. 4) that has some distinct properties like anti-septic, anti-oxidant, anti-inflammatory, wound-healing, against-angiogenic, and cancerous actions of phytochemical turmeric must be assigned to the yellow colorant (Shukla et al., 2014). It is a diferuloylmethane, a polyphenol derived from *Curcuma longa*, the most common Indian turmeric spice. This chemical is widely used for cancer therapy, and this compound has multiple other health benefits (Boyanapalli & Kong, 2015).

Curcumin’s anti-cancer activity has been related to its capability to control the expression of non-coding RNAs. Through investigating, it has been established that the miRNA-22 is up-regulated as curcumin and its target gene SP1 and ESR1 are less articulate (Shankar et al., 2013). In the circumstance of human pancreatic cells MIA PaCa-E and M, BxPC-3 to gemcitabine by inhibition of miR-21, gene factor NF-kB, COX-2 inactivation, and compounds found in their downstream, and by curcumin micro-RNAs (miR-200b and miR-200c) reactivation (Thakur et al., 2014). This bioactive molecule has been demonstrated to minimize the Bcl-2 expression in breast cells (MCF-7) cancer through enhanced regulation of the expression of miR-15a and 16. Another research shows that in cancer of human colon cells RKO and HCT116 suppression in miR-21 level, which is highly observed in many human uneven growths and enhance influx, malignant growth is controlled through this phytochemical (Cai et al., 2021).

Cell death protein 4 (Pcd4) for colorectal cancer is a suppressing mechanism (Thakur et al., 2014) expression stabilized through

**Table 1**  
Classes and sources of phytochemicals for treatment of various cancer.

Sr. No	Classes	Phytochemical	Source	Cancer Type	Modulation Effect	References
1	Polyphenol	Curcumin	Turmeric	Breast, lung, colon, prostate	↑miR-15a & miR-16 (breast) ↑ miR-15a, miR-16, and miR-186* ↓ miR-21 (colon)	(Boyanapalli & Kong, 2015; Debnath et al., 2017) (Debnath et al., 2017; Thakur et al., 2014)
		Resveratrol	In the skin of grapes, blueberries, raspberries, mulberries	Colon, acute lymphoblastic leukemia, breast	acetyl group removal from FOXO (in prostate cancer) ↑miR141, miR663, and miR-200c ↓miR-17, miR-21, miR-25, miR-92,2, miR-103-1, and miR-103-2	
2	Isothiocyanate	Sulforaphane	Broccoli	Colon, prostate	DNMT1 activity in CaCo-2 ↓ (colon) DNMT1 and DNMT3b ↓ (prostate)	(Thakur et al., 2014)
3	Tannin (phenolic compound)	Ellagitannins	Berries	Colorectal cancer	miR-let-7e, miR-370, miR-373* and miR-526b ↑ let-7a, let-7c, let-7d ↓	(Debnath et al., 2017; Thakur et al., 2014)
4	Carotenoid	Astaxanthin	shrimps, salmon, crabs	Prostate	↑ miRNAs miR-375 and miR-487b	(Debnath et al., 2017)
5	Terpenoid	Lycopene	Tomatoes	Prostate	↑ miR-let-7f-1 ↓ protein kinase B (AKT2)	(Debnath et al., 2017; Thakur et al., 2014)
6	Flavonoid compound	Quercetin	Citrous fruit and buck wheat	Lung, breast, renal, colon	↑ let-7 ↓ miR-27a ↑let-7a & c, miR-200b-3p & miR-142-3p	(Debnath et al., 2017)



**Fig. 4.** Structure of phytochemicals.

this phytochemical. Treatment through this plant extracted chemical enhanced HDAC1- 4-5 & 8 but less HDAC-3. Activity of HDAC, levels of H3K27me3, Neurog1 promoter region binding was decreased after treatment, recommending potential of phytochemical to express again until any other gene silenced through epigenetic alteration in cancer. This phytochemical has multiple

benefits with epigenetic modification to treat cancer (Thakur et al., 2014).

#### 4.1.2. Resveratrol

It is also a plant-based extract, and its source is skin of grapes seed and skin (Debnath et al., 2017) blueberries, raspberries, mul-

berries, (Subramanian et al., 2016) cranberries, peanut (Shankar et al., 2013). Resveratrol (3,5,4'-trihydroxystilbene) is a polyphenol discovered in peanuts, seeds of grapes, and peel of grapes. Numerous health advantages of resveratrol have been recognized to act against oxidative stress, against inflammation, show anti-cancerous activity, and cardio-protective properties. Regulation of MAPK/ERK1/2 signaling and expression of miRNA in colon cancer have shown anti-cancerous effect by the combination of this phytochemical resveratrol and 5-fluorouracil (Debnath et al., 2017).

Resveratrol showed weak DNMT hindering performance in cells of breast cancer MCF7 and was not able to reverse methylation of many genes have role in the suppression of tumor. Downregulation of many miRNAs through phytochemicals leads to the treatment of cancer (Thakur et al., 2014). The chemical extracted from the plant strongly affects cells' signaling system involved in cell formation, cell division, angiogenesis, apoptosis, and metastasis. Resveratrol has been reported to modulate the survival of cells and apoptosis by eliminating the acetyl group from the FOXO prostate cancer transcription factor. It was suggested that the combinatorial effect of this chemical along tea polyphenol could suppress the progression of skin cancer in mice through suppression of activated pathways MAPKs and p53 (Shankar et al., 2013).

## 4.2. Isothiocyanate

### 4.2.1. Sulforaphane

This chemical present in sprouts of broccoli, kale, and cabbage (Gavamukulya et al., 2014). This is also a plant-derived phytochemical sulforaphane (SFN), isothiocyanates (Shukla et al., 2014) mostly found in kale, sprouts, broccoli, and cabbage, extensively researched against the anti-cancerous effect. This xenobiotic metabolism has been observed and affects cell rotation retention and programmed death of cells in different cancer cells of humans (Dinkova-Kostova & Kostov, 2012; Khor et al., 2006).

SFN also can regulate the epigenetic modulations in cancer cells like other plant polyphenols. DNMT1 activity in CaCo-2 colon cancer cells undergo down-regulation, it resulted in the form of treatment of human colon cancer (Thakur et al., 2014). Phytochemical SFN was exposed to DNMT1 & 3b level inhibition for treating cancer (prostate) in humans (Mukhopadhyay et al., 2012).

## 4.3. Tannin (phenolic compound)

### 4.3.1. Ellagitannins

This phytochemical is present in a few foods like fruits and nuts, including pomegranate, strawberries, blackberries, almonds, walnuts, and raspberries. This chemical is used in medicine due to its anti-oxidant, against cancer, and anti-inflammatory (Berghe, 2012). This bioactive molecule regulates many signaling pathways and transcriptional factors in their potential to stop proliferation and influence apoptosis of cancer cells (Link, Balaguer, & Goel, 2010).

The use of ellagitannins, that is the extraction of the plant (*Balanophora japonica*), to impede the progression of HepG2 cell and modify the expression of many microRNAs has been shown to treat liver cancer. This phytochemical treatment, specifically enhanced expression of some micro-RNAs such as miR-let-7e, miR-370-373\*, and miR-526b and ellagitannins, also reduces the expression of let-7a, let7c, let-7d. All these non-coding RNAs/miRNAs are associated with those genes playing role in the proliferation and differentiation of cells (Thakur et al., 2014).

## 4.4. Carotenoid

These are plant-derived natural chemicals with yellow, red, and orange color examples of some carotenoids like alpha-carotene,

beta-carotene, astaxanthin, lycopene, and lutein. Through studies, it has been shown that carotenoids can be used in cancer prevention.

### 4.4.1. Astaxanthin

**Astaxanthin** (3,3'-dihydroxy- $\beta$ -carotene-4,4'dione) is present in crabs, shrimps, salmon, and Asteroidean's red pigment. Studies have shown that its anti-inflammatory, anti-oxidant and anti-cancer effects are beneficial for it. This phytochemical has many medical applications. Astaxanthin (100 mg kg<sup>-1</sup>) remarkably involves stopping the PC-3 growth in xenograft prostate cancer through a upsurge in the number of apoptotic cells through a surge in apoptotic cells and tumor tissue rise in tumor suppressor miRNAs level, miR-375 and 487b (Debnath et al., 2017).

## 4.5. Terpenoid

### 4.5.1. Lycopene

The decline in the proliferation of cancer and the rise in the apoptotic death of cells has been noted as an anti-cancer in various kinds of human cancers, comprising prostate, breast, and colon cancer. Recently, it was noted that lycopene involves the suppression of proliferation in cancer cells. In the case of prostate cancer increased the apoptotic process through miR-let-7f-1 level upregulation and protein kinase B (AKT2) expression down-regulation (Debnath et al., 2017).

## 4.6. Flavonoid compound

### 4.6.1. Quercetin

This phytochemical has anti-oxidant properties, available in vegetables, fruits, grains, leaves, and supplements (Shankar et al., 2013). The preservative consequences of this chemical on human fitness are conciliated by multifarious, pleiotropic effects from an epigenetic opinion. In recent research, the goal of controlling non-coding RNA expression was to obtain a therapeutic perspective in cancerous cells (Busch et al., 2015).

Quercetin can raise the expression of micro RNA (miR-146a) in cancerous breast cells of humans, similarly, miR-155 expression was slow-down in murine macrophages. The miR-146a upregulation induced the stimulation of Toll-like receptor 4 that mediates the factor NF- $\kappa$ b; these receptors are a carrier of inflammation. The impact of phytochemical was also detected in many kinds of human cancer cell lines in pancreatic adenocarcinoma marking the higher regulation of all these let-7a & c, miR-200b-3p & miR-142-3p (Cione et al., 2020).

## 4.7. Anticancer agents obtained from marine organisms

Decades ago, the separation of C-nucleosides from the Caribbean sponge *Cryptotheca crypta* laid the groundwork for the development of cytarabine, the first marine-derived anticancer drug. Cytarabine is being utilized in the treatment of leukemia and lymphoma patients. One of its fluorinated derivatives, gemcitabine, has also been approved for treatment in pancreatic, breast, bladder, and non-small-cell lung cancer patients. Cytarabine was primarily used in poly chemotherapy, and it was the foundation of the most commonly used regimens, such as the salvage therapy MEC (mitoxantrone, etoposide, and cytarabine), DHAP (dexamethasone, cytarabine, and cisplatin), and ESHAP (etoposide, methylprednisolone, high dose cytarabine, and cisplatin) (Schwartzmann, da Rocha, Berlinck, & Jimeno, 2001).

### 4.7.1. Tunicate Derivatives:

Didemnin B, aplidine, and ET-743 are all antitumor chemicals originating from marine sources. Didemnin B is a cyclic depsipep-

tide isolated from *Trididemnum solidum*, a tunicate. It has demonstrated excellent antitumor efficacy in both human tumor models in vitro and tumors growing in athymic mice (Rinehart, 2000). Patients with various solid tumors or non-Hodgkin lymphoma were given a brief intravenous infusion of didemnin B every three weeks in early clinical studies, and antitumor effects were noted. Aplidine appears to be more active in preclinical models than didemnin B, and there has been no evidence of life-threatening neuromuscular toxicity so far. Because aplidine's antitumor activity appears to be stronger in preclinical models following extended drug administration (Weiss et al., 1994).

#### 4.7.2. Dolastatins

Dolastatins are cytotoxic cyclic and linear peptides produced from *Dolabella auricularia*, a type of sea hare. Dolastatins 10 and 15 are minute peptides, with dolastatin 10 is particularly effective in vitro and inhibits microtubule assembly, causing cells to aggregate in metaphase. In early clinical studies, Dolastatins 10 caused bone marrow toxicity, as well as local discomfort at the injection site and mild peripheral neuropathy (Pathak, Multani, Ozen, Richardson, & Newman, 1998).

#### 4.7.3. Bryostatins

*Bugula neritina* is a marine bryozoan that produces bryostatin, a macro cyclic natural lactone. It affects the activity of protein kinase C (PKC), lacks tumor-promoting action, and induces differentiation. It also possesses immune-modulatory characteristics, such as inducing cytokine release and increasing the number of tumor-specific lymphocytes (Hornung, Pearson, Beckwith, & Longo, 1992).

#### 4.8. Preventive role of phytochemicals in cancer

To prevent cancer in healthy individuals by using natural, biological and synthetic means is called as chemoprevention. These compounds prevent the progression of cancer by enhancing DNA damage. Capsaicin is phytochemical having chemo preventive role, it binds to TRPV1 receptor. The activation of the activator protein 1 (AP-1), nuclear factor kappa B (NF- $\kappa$ B), and signal transducer and activator of transcription 3 (STAT3) signaling pathways, which are responsible for tumor growth, is blocked by capsaicin therapy (Sung, Prasad, Yadav, & Aggarwal, 2012). Capsaicin has also been demonstrated to produce reactive oxygen species (ROS), depolarize mitochondria, and reason of cell cycle arrest, which leads to apoptosis. Capsaicin inhibits bladder cancer cell migration by binding directly to sirtuin 1 (SIRT1) and inhibiting SIRT1 deacetylase. Capsaicin-induced apoptosis in pancreatic cancer cells was linked to  $\beta$ -catenin signaling suppression (S. K. Sharma, Vij, & Sharma, 2013).

Lycopene is an antioxidant and its anticancer activity has been reported, research has reported that higher intake of lycopene is associated with decrease occurrence of prostate cancer. Lycopene accumulate in prostate tissues and responsible for anti-prostate cancer activity, cell cycle arrest and apoptosis in prostate cancer cells. By inhibiting NF- $\kappa$ B signaling lycopene inhibit prostate and breast cancer cells (Assar, Vidalle, Chopra, & Hafizi, 2016). Cucurbitacins are tetracyclic triterpenoids is an active anticancer agent. In lung cancer, colorectal cancer, breast cancer and neuroblastoma it inhibits STAT3 signaling. In metastatic breast cancer Cucurbitacins is responsible for inhibition of VEGF/FAK/MMP-9 signaling (Sinha et al., 2016). By inhibiting HER2-integrin signaling it prevents the growth of tumor in breast. The inhibition of HER2-integrin signaling is responsible for the down regulation of integrin  $\alpha$ 6 and integrin  $\beta$ 4. In pancreatic cancer Cucurbitacins causes the inhibition of JAK-STAT pathway (Pan et al., 2009).

Benzyl isothiocyanate is natural compound which causes apoptosis in pancreatic cancer cells by inhibition of STAT3 signaling

mediated HIF-1 $\alpha$ /VEGF/Rho-GTPases. Phenyl isothiocyanate persuades ROS generation in chronic lymphocytic leukemia cells (Lai et al., 2010). Phenyl isothiocyanate in combination with paclitaxel inhibit tumor growth in breast cancer by apoptosis and cell cycle arrest (Liu et al., 2016). Isoflavones have potential health benefits and those obtained from genistein have reported anticancer activities, they prompt apoptosis by inhibition of IGF-1R/p-Akt signaling in breast cancer (Chen et al., 2015).

#### 5. Epigenetics activities of phytochemicals in the treatment of cancer

The application, before the disease occurs clinically, of dietary or pharmacological substances to avoid, prevent or reverse carcinogenesis indicates the use of cancer chemoprevention. Drug use includes early and potentially reversible epigenetic modifications which inhibit some molecular steps in cancer (Wagner, Terschluesen, & Rimbach, 2013). A fruit and vegetable-rich diet could prevent a minimum of 20% of all cancer. For the 175 small molecules accepted for cancer therapy, more than 49% have been or are derived from natural products (Newman & Cragg, 2016). Natural products containing bioactive components are gaining popularity in cancer prevention and treatment due to their compatibility with biological target sites and low toxicity to normal cells (Remely et al., 2015). Although specific molecular pathways remain elusive, it has become clear that plant chemicals can modulate epigenetic events in human health. Some polyphenols and organosulfur compounds have anti-tumor effects and modulate the underlying pathways in human health. They form a connection between the genome and the environment with physiological concentration accuracy (Pop, Enciu, Tarcomnicu, Gille, & Tanase, 2019). Recent findings have shown that the crucible between cancer metabolism and the epigenome has occurred. Therefore, the metabolism and enzymes that provide these key compounds are important for maintaining and adapting epigenome. The methionine-deficient diet significantly reduces SAM levels, resulting in decreased DNA and histone methylation impacting gene expression (Parasramka, Ho, Williams, & Dashwood, 2012). Dietary phytochemicals can exercise chemoprevention by modulating indirectly DNMT activities by adjusting the SAM / SAH ratio and influencing cellular metabolism intervention. The flavanol-rich diet has catechol-structured polyphenols that can be methylated using SAM as the methyl-donor by catechol-O-Methyltransferase (COMT) (Bistulfi, VanDette, Matsui, & Smiraglia, 2010). Because of their compatibility with biological target sites and low toxicity to normal cells, natural products containing bioactive components are gaining popularity in cancer prevention and treatment (Zhu, Wu, Wang, Cai, & Conney, 2010).

Several studies have shown that some food phytochemicals inhibit tumor growth by influencing pathways of epigenetic signaling (Remely et al., 2015). Dietary phytochemicals with DNA-methylation epigenetic modulation activities can be divided into three based on the mechanism of their action;

1. The phytochemical module the DNMTs activities by manipulating the methyl pool. and
2. Some of the most promising bioactive natural product candidates for cancer prevention and therapy are phytochemicals that direct DNMT enzyme inhibitors.
3. The phytochemical products contribute to methyl groups and act as co-substrates in the DNMT method (Ho, Beaver, Williams, & Dashwood, 2011).

Polyphenols are the largest group of secondary plant metabolites present in fruit, vegetables, cereals, and beverages. Phenol



acid lignans, stilbenes, and flavonoids are among the polyphenol groups (Carlos-Reyes et al., 2019; Hardman, 2014). Some epigenetic mechanisms include DNA status modulation, histone methylation, and acetylation, may be used to medium the chemical prevention of flavonoids (Y. Guo et al., 2018). For example, kaempferol does not affect bladder and CRC activity but inhibits DNMT1 and DNMT3B. Some flavonoids have an inhibitory DNMT activity (Banerji, 2017). Genistein is the most active DNMT inhibitor in esophageal squamous carcinoma and prosthodontic cells capable of reactivating silent gene methylation including rap, p16INK4a, and MGMT (Fang et al., 2005). The use of genistein in the treatment of benign and malignant brain tumors reduces the activity of human telomerase reverse transcriptase (hTERT), the over-expressed catalytic subunit of telomerase in 90% of cancers through epigenetic modulation involving decreasing DNMT expressions and coexisting with H3K9me3 hyper-methylation and H3K4me2 chromatin-brand hypo-methylation (Li, Liu, Andrews, & Tollefsbol, 2009).

Sulforaphane is in the Brassicaceae family and is the most important chemical prevention agent in organosulfur compounds in the isothiocyanate (ITC) community. Research have proved that SFN is an effective chemo-preservative agent in many cancers, inducing anti-proliferative, anti-inflammatory, anti-angiogenic, anti-oxidant, and differentiation induction, apoptosis, and cell cycle arrest (Kwon, Barve, Yu, HUANG, & KONG, 2007). To suppress mitochondrial activity and lipid peroxidation, SFN induces the chemical preventive effects of phase I enzymes CYP and phase II detoxified enzymes. An epigenetic agent that can control COMT expression to affect estrogen metabolism has been found in a recent research to show that SFN activates the No<sub>2</sub> way in cells with breast cancer (Cao et al., 2018). Recently, SFN has become increasingly interested in manipulating epigenetic procedures by aiming key epigenetic modulators such as DNA methyltransferases and HDACs, resulting in local or global changes in epigenetic char-

acteristics and subsequent gene transcription and expression levels (Khan, Rath, Adhami, & Mukhtar, 2018). Additionally, SFN modules demethylation of DNA by downregulation of DNMT1 and DNMT3 B expression, contributing to cyclin D2 gene promoter mediated demethylation and cancer cell expression (Hsu et al., 2011).

Sulforaphane modulates chemoprevention epigenetic pathways. Sulforaphane induces NRF2 gene activation and up-regulates anti-oxidant expression associated with cancer prevention mechanisms (Fig. 5). Collecting evidence suggests that sulforaphane can have at least partial effects on epigenetic mechanisms of anti-cancer properties. Sulforaphane is a well-defined DNMT and HDAC inhibitor that reduces gene-specific methylation of cancer cells by promoters while increasing total and promoter-specific histone acetylation. SFN can also modulate several microRNAs' expression, and decreased 6-adenosine RNA methylation has been correlated with mRNA levels (Pop et al., 2019).

### 6. Modification of microRNA expression through phytochemicals for the treatment of cancer

Studies recommend that micro RNAs are vital for cancer treatment due to their tumor-suppressive and oncogenic characteristics (Ramassone, Pagotto, Veronese, & Visone, 2018). It is considered one of the attractive mechanisms in many activities against cancer for the various phytochemicals (Srivastava, Arora, Averett, Singh, & Singh, 2015). Different phytochemicals can regulate miRNA at multiple stages and many mutations in the mechanism of either rise or fall in the micro RNA level (Sato, Tsuchiya, Meltzer, & Shimizu, 2011). Scientists have explored and described that treatment through phytochemical (Resveratrol) knowingly raises the Ago2 expression and outcome in the form of an increased miRNA level with a tumor-suppressive ability like miR-16,141,143 and miR-200c in cells (MDA-MB-231). Moreover, treatment through plant-

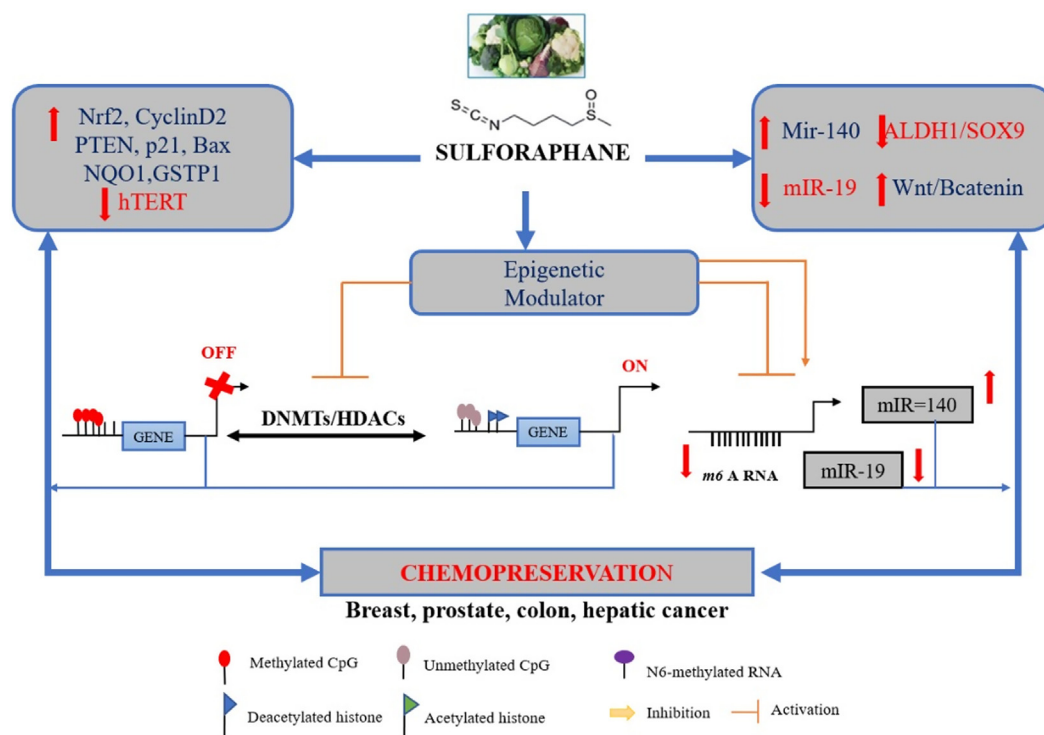


Fig. 5. SFN as bioactive molecule from natural sources that can modulate epigenetic mechanism.

derived compound Resveratrol showed that the upregulation of miR-663 and pre-miR-663 by intermitting with the drosha resolved management of pri-miR-663 that expressed the miR-155 inhibition, which is highly expressed in various cancers (Tili et al., 2010). Moreover, downregulation of expression of non-coding RNA also interferes in the tumorigenesis initiation and upregulation, the fundamental processing of miRNA downregulation in human cancer is still mainly unidentified (Deng, Calin, Croce, Coukos, & Zhang, 2008). Many plants extracted chemicals that we can use to modulate the expression of non-coding/ miRNA in cancer.

Recent studies have shown that phytochemicals and TCHMs can reverse changes in epigenetics in disease prevention and be involved in biological process regulation (Zhou, Yang, & Kong, 2017). MicroRNAs and specific signaling pathways control these processes (Wnt/ $\beta$ -catenin, Notch, Sonic hedgehog, COX-2, EGFR, MAPK-ERK, JAK-STAT, Akt / PI3K / mTOR, NF- $\kappa$ B, AP-1, etc.). Phytochemicals and dietary polyphenols are essential for preventing cancer metastasis and other cancer properties because they modulate cancer-related miRNAs (N. Kashyap et al., 2019).

A variety of cellular processes can be affected by phytochemicals such as proliferation, apoptosis, cell cycle regulation, angiogenesis, inflammation, and DNA repair. Phytochemicals can modulate microRNAs and their target genes with cancer-related chemo-preventive mechanisms (Babashah, Bakhshinejad, Birgani, Pakravan, & Cho, 2018). Some phytochemicals control miRNA expression in numerous cancers (Debnath et al., 2017). Garcinol, Curcumin (Cione et al., 2020), Tea polyphenols, Ellagic acid, Isoflavonoids genistein, Indole-3-carbinol (Christensen & LeBlanc, 1996), Pomegranate polyphenols, Resveratrol (Cione et al., 2020), EGCG, Genistein, Quercetin (Cione et al., 2020; Neto, 2007), Camptothecin and DIM.

Only a few studies explore phytochemical anti-tumor efficacy in clinical trials controlling miRNA expression. BR-DIM is curiously expressed 3, 3'-diindolylmethane (DIM) resulting from I3C digestion. The expression of miRNA-34a tumor suppression in human prostate cancer was evaluated by demethylation of the promoter region miR-34a following treatment with BR-DIM. Increased expression mir 34a correlated to a decreased expression in androgen receptor (AR), with low expression miR-34 linked to a notch 1 or CD44 upregulation (Samec et al., 2019).

Besides, a randomized study based on the intake and upregulation of oncogenic miR-21 and miR17-92 cluster high red meat (HRM) as compared to butyrylated resistant starch (HRM + HAMS) supplementation in healthy volunteer rectal mucosa was conducted. Grounded on the findings, the study showed that miR17-92 cluster expression was down-regulated, but miR-21 levels remained higher after HRM + HAMS intervention relative to basal expression. Modifications in miRNA expression in reaction to the HRM diet have been meaningfully correlated with lower regulation of their target mRNAs encoded with the CDKN1A gene (Humphreys et al., 2014).

In the cancer progression mechanism, scientists analyzed the expression of 800 miRNAs. Many of miRNAs like miR-29a-3p, -223-3p, -142-3p, -150-5p, -590-3p, -219-5p, -188-3p, -3168, miR-34a, -2110, -759, -891b, and -4421 modulation were induced by Soy Input (Hargraves et al., 2016). The target genes of miRNAs include TP53, AGO2, and DDX20, which are important to cell development, invasion, and proliferation regulation. The target genes of miRNAs are TP53, AGO2, and DDX20 and play a crucial role in cell growth, invasion, and proliferation control (X. Guo et al., 2016).

MDA-MB231 cancer-cell effects of mango polyphenols were reported as decreasing metastasis protein expression, VEGF, increased cleavage of caspase-3, PARP (poly ADP-ribose polymerase) and cytochrome expression C, and decreased Bcl-2 (B-

cell lymphoma 2). Additionally, decreases in PI3 K, Akt, mTOR, HIF- $\alpha$ , and increases in PTEN were seen as tumor abnormalities consistent with suppression after administration of mango polyphenols. Finally, while miR-126 was not significantly inhibited by miR-21, a key oncomiR that has been widely reported to be overexpressed in various cancer cells, even though its function is still unknown (Arbizu-Berrocal et al., 2019).

Sanguinarine, a plant alkaloid found in the root of *Sanguinaria canadensis*, has been used as a miRNA regulator, as a miR-16 modulator, an established tumor suppressor for various cancers in humans. Zhang et al. (2019) found that among 140 substances, the sanguinarin exhibited a regulatory impact on miR-16. Downregulation was observed of the target genes miR-16, cyclin D1, and Bcl-2. Sanguinarin miR-16 activation resulted in phase G1/S cell cycle arrest, while ROS production induced hepatocellular carcinoma cell apoptosis. Such results suggest that phytochemicals are potential regulators of miRNA and can be an effective chemo-preventive strategy for cancer if the development of cancer-related miRNA is modulated, even though the direct interaction between phytochemicals and DNA resulting in miRNA production is not yet clear (Koh, Ho, & Pan, 2019). Numerous clinical trials have demonstrated the potential to treat antineoplastic with natural bioactive plant or food supplement compounds. Still, none of the trials emphasis on the role of miRNAs in carcinogenesis (Srivastava et al., 2015).

## 7. Effect of phytochemicals on the metabolism of cancer cells

Flavones and isoflavones and their derivatives, such as flavanols, are active against numerous other neurodegenerative products with enormous cyclic activities, such as anti-cancerous, anti-inflammatory (Muntean, Sturza, Pavel, & Duicu, 2018). In particular, the anti-cancer effects of these compound groups were studied to take advantage of their anti-cancer activity and develop a highly effective and low-toxic cancer drug (Abotaleb et al., 2019). In particular, numerous phases of development and cancer cell growth have been affected by varying signals and metabolic processes through which the modification principals to cancer (D. Kashyap et al., 2019). The dose-dependent effect on this flavanol has been shown to contribute to low and high concentrations of anti-oxidants and prooxidants. Cancer cells, in contrast to normal cells, prefer glycolysis over oxidative phosphorylation under normal conditions (Bandres et al., 2009). It has been mentioned earlier. Targeting specific enzymes and signaling molecules to prevent glycolysis is also seen as a potent treatment for cancer control (Hamilton et al., 2018). Such quercetin effects have been expressed as a decrease in glucose efflux and lactate production in breast cancer cells. Quercetin prevents breast cancer cell metastases by inhibiting glycolysis, and thus the fabrication of lactic acid as a step in the glucose and acidic environments are two important requirements for cancer cell survival, proliferation, and progression (Rouhi, Mager, Humphries, & Kuchenbauer, 2008). Quercetin is known to be activated by inactive Akt-mTOR pathways, which induce autophagy that inhibits metastasis (Rivera, Castillo-Pichardo, Gerena, & Dharmawardhane, 2016). The most popular flavanol originate in many fruits and vegetables like apple, kiwi, grape, onion, strawberry (2-(3, 4-dihydroxyphenyl), and green tea, such as 0.1 to 539 mg / g, is Fisetine. There has been a extensive variety of biological events, including anti-cancer, neuroprotective, and anti-oxidants. Fisetine has also demonstrated beneficial effects on cancer cell metabolism and suggests it is directed explicitly to PKI3-Akt - mTOR signaling pathways and thus decreases expression in cancer and metabolic pathways (Sundarraj, Raghunath, & Perumal, 2018).

## 8. Conclusions and perspectives

Natural products are becoming more popular due to their inexpensive cost and reliability over existing medications' adverse effects. Researchers are stepping up their attempts to develop phytopharmaceuticals that can treat severe metabolic disorders, such as cancer. Bioactive phytochemicals and formulations could be used to generate safer anticancer medicines. For this goal, several plants and their constituent phytochemicals have been examined, but only a handful have made it to the clinical stage. Druggable versions of anticancer phytochemicals with appropriate bioavailability must be created. Traditional herbal preparations have a stronger medical impact than the identical phytochemical/molecule in its purest form. As a result, therapeutic intervention based on the combination of anticancer compounds has the potential to produce potent and successful therapeutic results. In recent years, a considerable contribution has been made to our understanding of epigenetic modifications in cancer growth. Clinicians and the pharmaceutical industry have been actively motivated to develop epigenetic biomarkers and therapeutic strategies for detecting and treating cancer through their reversible and complex existence. Nonetheless, before our present understandings can be completely extended in the clinical area, we need to tackle the complexities of epigenetic processes, including interplays of the various epigenetic roles for gene transcription and the hereditary variations of epigenetic regulators. The specific mechanism by which phytochemicals act as anticancer agents is still under investigation. They have a vast and complex variety of effects on a cancer cell's nuclear and cytosolic components. They can absorb reactive oxygen species (ROS) directly or enhance antioxidant enzyme activity in a changed cell. A phytochemical can inhibit the metabolic conversion of a pro-carcinogen or prevent malignant transformation of an initiated pre-neoplastic cell. They can also influence biological and signaling activities involved in cancer cell proliferation, invasion, and metastasis. Pomegranate ellagic acid causes apoptosis in prostate and breast cancer cells and prevents cancer spread in a variety of cancer types. Ornithine decarboxylase, an enzyme that instructs the cell to proliferate faster and avoid apoptosis, is suppressed by epigallocatechin gallate (EGCG). Luteolin prevents the transition between epithelial and mesenchymal cells. Flavones, isoflavones, and lignans stop estrogen from attaching to cancer cells, reducing their proliferation. Despite the positive pharmacological activity of different phytochemicals, clinical translation of their therapeutic benefits is problematic, particularly with polyphenols. Many of these chemicals have little water solubility or can't be kept in circulation effectively. Pharmacological concentrations in blood or tumour tissues can be hampered by low gastrointestinal absorption, high metabolism, chemical degradation, and quick clearance. The flavonoids quercetin and EGCG usually achieve low micro molar concentrations in blood, which can be enough for cytoprotective effects but are insufficient for potent antitumor activity. Significant effort has gone into designing delivery systems that can overcome these critical disadvantages by boosting bioactive phytochemical stability and solubility, improving oral bioavailability, and precisely targeting tumor cells.

Similarly, modifications of miRNome to the regular cell counterpart have been described in cancer cells. Recently, the discovery of epigenetic regulation of miRNAs and epi-miRNAs' presence have shown that miRNAs and epigenetics are gene regulation intertwined biological effectors. Understanding the miRNome-epigenome correlation will contribute to a better understanding of gene regulation and human cancer, which allows the translation of this information into new therapies for cancer patients. Furthermore, a broad variety of epigenetic regulators are reported to affect most phytochemicals. The knowledge of the global dynamics of

epigenetic changes caused by phytochemicals would also help to refine cancer prevention and treatment strategies.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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