GESA
GLOCAL ENVIRONMENT & SOCIAL ASSOCIATION

International Journal of Biological Innovations
http://ijbi.org.in | http://www.gesa.org.in/journals.php
https://doi.org/10.46505/IJBI.2025.7106
IJBI 7(1): 41-53 **(2025)**
E-ISSN: 2582-1032

PHYTOCHEMICALS: KEY MODULATORS TO REVERSE EPIGENETIC CHANGES

Abhimanyu Kumar Jha[1,2,3]

[1]Eudoxia Research University, USA
[2]Eudoxia Research Centre, India
[3]Department of Biotechnology, School of Biosciences and Technology, Galgotias University, Greater Noida (U.P.), India

*Corresponding author: abhimanyujha630@gmail.com

Article Info:
Review Article
Received
20.01.2025
Reviewed
27.02.2025
Accepted
14.03.2025

Abstract: Cancer remains a major global health challenge, with epigenetic modifications playing a crucial role in its initiation and progression. Unlike genetic mutations, epigenetic changes such as DNA methylation and histone modifications are reversible, making them promising targets for therapeutic intervention. This review highlights the role of natural compounds, particularly phytochemicals, in modulating epigenetic pathways involved in cancer development. Flavonoids, polyphenols, and other bioactive compounds exhibit anticancer properties by targeting key epigenetic regulators, including DNA methyltransferases (DNMTs) and histone deacetylases (HDACs). These natural 'epi-drugs' can reverse aberrant DNA hypermethylation, reactivate tumor suppressor genes, and modulate histone acetylation, thereby inhibiting cancer cell proliferation and metastasis. Compounds such as epigallocatechin gallate (EGCG), curcumin, and resveratrol have demonstrated significant epigenetic effects in preclinical studies. However, challenges such as low bioavailability, poor pharmacokinetics, and limited clinical validation hinder their widespread application. Advances in drug delivery systems, including nano-formulations and encapsulation strategies, may enhance the therapeutic efficacy of these compounds. This review underscores the potential of phytochemicals as epigenetic modulators in cancer prevention and therapy while emphasizing the need for further research to optimize their clinical applicability and therapeutic outcomes.

Keywords: Cancer, DNA methylation, Epigenetic modulation, Natural epidrugs, Phytochemicals.

Cite this article as: Jha A.K. (2025). Phytochemicals: Key modulators to reverse epigenetic changes. *International Journal of Biological Innovations*. 7(1): 41-53. https://doi.org/10.46505/IJBI.2025.7106

INTRODUCTION

Cancer is defined by the abnormal and uncontrolled growth of cells that form malignant clones, invade nearby tissues, and eventually metastasize to distant organs (Verma, 2017; Shoaib *et al*., 2023). It is the second leading cause of death worldwide, with millions of new cases reported annually. In 2020, approximately 19.3 million people were diagnosed, and nearly 10 million died from the disease (Sung *et al*., 2021). Despite advancements in diagnostic methods and therapeutic strategies, the cancer remains a

significant global health challenge, particularly in low- and middle-income regions (Baig *et al*., 2019). Cancer progression typically follows multiple stages: stage I (localized tumors), stages II and III (invasion into surrounding tissues or lymph nodes), and stage IV (metastatic disease) (Nikbakht *et al*., 2017; Farheen *et al*., 2025). Diagnosis commonly involves blood tests, immunohistochemistry, and advanced imaging techniques, including CT, MRI, and PET scans. Several risk factors are known to contribute to cancer development, including tobacco use (Masroor *et al.,* 2020; Kumar and Jha, 2023), excessive alcohol consumption, obesity, genetic predisposition, viral infections, chronic inflammation, and exposure to carcinogenic substances (Avgerinos *et al*., 2019; Agarwal and Jha, 2025).

Current cancer treatment approaches rely on surgery, radiation therapy, chemotherapy, immunotherapy, and combinations such as chemoradiotherapy (Khandia and Munjal, 2020). However, these treatments often lead to side effects ranging from mild to severe, impacting the skin, blood, kidneys, gastrointestinal system, and nervous system, with potential risks of hepatotoxicity, cardiotoxicity, and neurotoxicity (Sokolenko and Imyanitov, 2018; Schirrmacher, 2019). Key characteristics of cancer include uncontrolled proliferation, invasion, migration, hypoxic conditions, angiogenesis, and abnormal vascular functions. Several biomarkers are associated with these processes, such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), integrin μ***v***β***3,*** carcinoembryonic antigen (CEA), folate receptors, transferrin receptors, somatostatin receptors, and prostate-specific membrane antigen (PSMA). Dysregulated signaling pathways, including EGFR, cyclooxygenase-2 (COX-2), nuclear factor κB (NF-κB), interleukins (IL-6, IL-1), cyclin proteins (D1, E), VEGF, and anti-apoptotic factors (Bcl-2, Bcl-XL, survivin, XIAP), play pivotal roles in tumor progression (Multhoff *et al*., 2012).

Chronic inflammation is a critical contributor to cancer development, facilitating tumor growth, invasion, and metastasis. Inflammatory mediators such as hypoxia-inducible factor-1 (HIF-1), signal transducer and activator of transcription 3 (STAT-3), NF-κB, IL-6, IL-1, and tumor necrosis factor (TNF) are key players in this process (Saha *et al.,* 2020). Persistent inflammation promotes immune evasion, prevents apoptosis, enhances vascularization, and supports metastatic spread. Early-stage cancer development is often influenced by reactive oxygen and nitrogen species and cytokines from tumor-infiltrating immune cells, which trigger epigenetic modifications and silence tumor-suppressor genes (Jha *et al*., 2015, 2016). Tissue transglutaminase (TG2) further drives tumor progression by inducing epithelial-mesenchymal transition (EMT) through interactions with TGF-κ and NF-κB signaling, highlighting its strong link to inflammation-driven malignancies (Shoaib *et al*., 2023).

Epigenetic modification is an important factor in determining the level and timing of gene expression in response to endogenous and exogenous stimuli. There is also growing evidence concerning the interaction between epigenetics and metabolism (Sibuh *et al.,* 2023). Epigenetic mechanisms, including DNA methylation and histone modifications, are fundamental to regulating gene expression. Histone acetylation, facilitated by histone acetyltransferases (HATs), promotes gene activation, while histone hypoacetylation, mediated by histone deacetylases (HDACs), leads to gene silencing. Abnormal methylation patterns are a hallmark of cancer, often characterized by elevated expression of DNA methyltransferases (DNMT1, DNMT3a, and DNMT3b), which are significantly higher in cancerous cells compared to normal cells (Singh *et al*., 2022).

The altered expression of genes encoding HDACs and DNMTs has been associated with key cancer-related processes, such as uncontrolled cell growth, metastasis, cell cycle disturbances, and resistance to apoptosis (Shoaib *et al*., 2023). Recent evidence underscores the involvement of microRNAs (miRNAs) in cancer initiation and progression. Epigenetic regulation, including histone modifications, DNA methylation,

nucleosome remodeling, and non-coding RNA activity, plays a pivotal role in influencing the behavior of cancer cells.

In addition to genetic mutations, epigenetic changes provide an alternative pathway for the disruption of tumor suppressor gene function, contributing largely to carcinogenesis. The hypermethylation of CpG islands within promoter regions often results in the silencing of genes involved in cellular differentiation and tumor suppression, a process strongly linked to cancer development. For instance, the hypermethylation of the SMAD14 promoter has been associated with enhanced metastasis in gastric cancer (Xu *et al.*, 2020).

An imbalance between cell division and programmed cell death is a critical factor that supports the survival and advancement of cancer cells. Epigenetic suppression of genes involved in apoptosis contributes to tumor growth and metastasis. For example, the silencing of occludin, a key component of tight junctions is linked to cancer progression. Promoter hypermethylation is recognized as a prominent mechanism for gene silencing in various cancers, with numerous studies highlighting its strong association with disease development (Xu *et al.*, 2015).

PHYTOCHEMICALS AS EPIGENETIC MODULATORS AND EPIDRUGS AGAINST CANCER

Anthocyanidins

Anthocyanidins are the sugar-free forms of anthocyanins, which are naturally occurring pigments found in plants. They originate from the flavylium cation, an oxonium ion where hydrogen atoms are replaced by various substituent groups. Their coloration is influenced by pH levels, typically appearing red in acidic environments and shifting to purple, blue, or bluish-green under more alkaline conditions (Belwal *et al.*, 2020).

Anthocyanins

This study explores that demethylation is linked to black raspberry treatment in colorectal cancer, focusing specifically on anthocyanins. After three days of exposure, anthocyanins inhibited the activity and protein levels of DNMT1 and DNMT3B in HCT116, Caco2, and SW480 cell lines. These all also promoted demethylation of the promoter regions of CDKN2A, SFRP2, SFRP5, and WIF1, which are key upstream regulators of the Wnt signaling pathway. This epigenetic modification led to increased mRNA expression of certain genes, while -catenin and c-Myc, downstream effectors of the Wnt pathway, showed decreased expression alongside reduced cell proliferation. Confocal laser scanning microscopy confirmed the uptake of anthocyanins in HCT116 cells, with distinct localization patterns relative to DNMT1 and DNMT3B. Although DNMT3B is known to interact with c-Myc in mouse lymphoma, no such association was observed in HCT116 cells. These findings suggest that anthocyanins play a crucial role in the demethylation effects observed with black raspberry treatments in colorectal cancer (Zhang *et al.*, 2010).

Cyanidin

Cyanidin, a natural pigment found in foods like corn, has shown promise in protecting against heart damage and may help prevent cancer (Saclier *et al.*, 2020). A study looked at how cyanidin affects certain cell processes in breast cancer cells. The results showed that cyanidin could reduce the activity of an enzyme involved in DNA modification, but it didn't seem to change the way DNA or proteins are modified. This suggests that cyanidin might not be a strong modifier of cell processes on its own. However, the study mentions that eating foods with cyanidin over a long time might have a cumulative effect that could contribute to cancer prevention (Dormán *et al.*, 2016).

Pelargonidin

Pelargonidin, a natural pigment found in certain fruits, has been studied for its potential health benefits. Research suggests it may have a positive impact on cell processes. One study found that pelargonidin could reduce cell growth and activity in specific cell types, potentially by influencing certain antioxidant pathways (Karthi *et al.*, 2017). It also appeared to lower the levels of proteins involved in DNA modification and could

alter DNA methylation in a way that increases the expression of protective genes. Additionally, pelargonidin seemed to interfere with cell changes induced by a tumor-promoting substance. Another study explored how pelargonidin interacts with key proteins that regulate cell division and DNA modification. Computer modeling suggested that pelargonidin could bind to these proteins, potentially disrupting their function. This research indicates that pelargonidin might have multiple mechanisms of action and could be a promising agent for further investigation in cancer therapy (Li *et al*., 2019).

Delphinidin

Delphinidin, a vivid natural colorant prevalent in abundance within blueberries and various intensely pigmented fruits and vegetables, garners recognition for its antioxidative and anti-inflammatory attributes (Bonesi *et al*., 2018). Investigations propose it might safeguard cells against impairment, diminish inflammation, and avert detrimental mutations. Furthermore, it has demonstrated potential in impeding the dissemination of mammary carcinoma cells and could potentially disrupt the proliferation of nascent blood vessels, a process significant in neoplastic progression.

An investigation exploring delphinidin's prospective role in cutaneous malignancy prophylaxis centered on its capacity to activate a pivotal antioxidative defense mechanism within the organism. Delphinidin substantially repressed the genesis of precancerous cells within a murine model. This safeguarding consequence correlated with specific alterations in deoxyribonucleic acid, namely a diminution in DNA methylation at crucial loci within the regulatory region of a gene indispensable for antioxidative defense. This decline in DNA methylation corresponded with heightened activity of this protective pathway. Researchers additionally observed diminished quantities of proteins that participate in modifying DNA and histones, further substantiating the notion that delphinidin influences gene expression via epigenetic mechanisms. These outcomes imply that delphinidin can invigorate the body's inherent defenses against injurious oxidative stress by modulating DNA methylation and impacting associated protein concentrations, signifying its prospective merit in cutaneous malignancy prevention (Kuo *et al*., 2019).

Bioflavonoids

Bioflavonoids represent a specialized category within the broader group of flavonoids. These compounds are formed when two simpler flavonoid units connect, creating a more complex molecule. While still considered plant-based compounds, bioflavonoids are less widespread than other flavonoids and can serve as unique markers for specific plant types. Similar to other flavonoids, bioflavonoids possess a range of biological activities. Their notable antioxidant, anti-proliferative, and anti-inflammatory effects suggest potential applications in preventing or managing conditions such as atherosclerosis and related cardiovascular issues (Tabares-Guevara *et al*., 2017).

Amentoflavone

Amentoflavone is a natural biflavonoid consisting of two apigenin molecules linked at the 8 and 3' positions (3 , 8 -bi-apigenin). It occurs naturally in several plant species, including *Ginkgo biloba*, *Chamaecyparis obtusa*, *Hypericum perforatum* and *Xerophyta plicata*. By modulating the activities of the metabolic enzymes CYP3A4 and CYP2C9, which are crucial for processing specific pharmaceuticals, amentoflavone may affect drug efficacy and metabolism.

Zhaohui *et al*. (2018) investigated amentoflavone extracted from *Selaginella tamariscina*, a renowned traditional Chinese herb with potent anticancer effects, particularly in the treatment of malignant glioma-an aggressive brain cancer common in adults. Their findings revealed that amentoflavone significantly enhanced the expression of miR-124-3p in glioma cells compared to normal brain tissues. The compound reduced cell proliferation induced programmed cell death in a concentration-dependent manner and suppressed glycolysis in glioma cells by increasing miR-124-3p levels. The upregulation of miR-124-3p was linked to the

inhibition of DNMT1 through the transcription factor Sp1. This regulatory mechanism was driven by the activation of the ROS/AMPK signaling cascade.

Flavans

Flavans are naturally abundant compounds formed through the double reduction of flavanones. Many flavans exhibit lipid solubility and are typically found in the outer peel of fruits and the cutin layer on leaf surfaces. Some flavans function as phytoalexins, providing plants with defense mechanisms against fungal infections and insect attacks. Their concentration tends to be higher in unripe fruits compared to fully ripened ones. Flavans belong to a broad class of natural compounds characterized by the fundamental flavonoid structure (Mazimba and Keroletswe, 2016).

Flavanols

Flavanols are abundantly present in chocolate, cocoa powder, grapes, and various types of teas. These sources contain monomeric flavanols, such as catechin, epicatechin, epigallocatechin, gallocatechin, and their gallate derivatives, as well as their polymerized forms known as proanthocyanidins. Renowned for their potent antioxidant properties, flavanols play a crucial role in supporting diverse biological functions and influencing cellular signaling pathways (Lan *et al*., 2017; Bonetti *et al*., 2017).

Catechin, Epicatechin, and (-)-epigallocatechin-3-O-gallate

Lee *et al.* (2005) investigated the effects of tea catechins on DNA methylation by prokaryotic DNMT and human DNMT1. Catechin, epicatechin, and EGCG inhibited methylation in a dose-dependent manner, with EGCG being the most potent. Epicatechin suppressed methylation by increasing S-adenosyl-L-homocysteine formation, while EGCG directly inhibited DNMT activity. Molecular modeling confirmed EGCG's strong interaction with human DNMT1, supporting experimental results.

(-)-epigallocatechin-3-O-gallate

Zhang *et al.* (2015) reported that EGCG could reestablish the sensitivity of NSCLC cells to cisplatin (DDP) by reversing gene methylation. In A549/DDP cells, the combined administration of EGCG and DDP significantly suppressed cell proliferation, caused G1 phase cell cycle arrest, triggered apoptosis, and reduced DNMT and HDAC activities. The treatment also reversed hypermethylation and lowered the expression levels of GAS1, TIMP4, and ICAM1.

In vivo experiments showed that EGCG pre-treatment followed by DDP administration substantially inhibited tumor growth. The methylation of GAS1, TIMP4, ICAM1, and WISP2 was decreased, while their expression levels were elevated in the EGCG-treated groups. However, tumor growth suppression was only observed with the combination therapy. These outcomes suggest that EGCG pre-treatment restores DDP sensitivity by demethylating genes and reinstating their expression.

Flavanones

Flavanones form a smaller subgroup of dietary flavonoids but are notably present in tomatoes, oranges, and certain aromatic herbs like mint. In grapefruit, naringenin is the predominant aglycone, while hesperetin dominates in grapes and eriodictyol in lemons. These compounds are primarily concentrated in the solid parts of fruits, particularly within the white spongy layer known as the albedo and the membranes separating fruit segments. Their potential health-promoting properties have garnered significant scientific interest (Khan and Dangles, 2014).

Hesperetin

Hesperetin, a 4'-methoxy derivative of the flavanone eriodictyol, is closely related to hesperidin, its 7-O-glycoside form. Hesperidin is a naturally occurring flavanone glycoside and the primary flavonoid found in lemons and sweet oranges (Muhammad *et al.*, 2019). It is widely recognized for its strong antioxidant, anti-inflammatory, and anticancer activities. In a study by Hermawan *et al.* (2020), the researchers sought to explore the molecular mechanisms through which hesperetin may counteract chemo-resistance. Using molecular docking techniques, they compared hesperetin's effects with those of erbB receptor inhibitors. The results revealed that both hesperetin and these inhibitors targeted similar mRNA expressions,

indicating their capacity to inhibit key molecular factors such as ABL1, MLH1, and DNMT38, suggesting hesperetin's potential as a therapeutic agent (Hermawan *et al.,* 2020).

Hesperidin

Citrus fruits are a natural source of hesperidin, a flavanone glycoside, with hesperetin being its aglycone form. The name "hesperidin" originates from "hesperidium," a botanical term for citrus fruits. Initially identified in the white inner layer of citrus peels, hesperidin is believed to play a role in plant defense. This compound possesses diverse pharmacological properties, particularly antioxidant and anti-inflammatory effects. Notably, its chemopreventive potential has been demonstrated in both in vitro and in vivo pre-clinical cancer models. To assess whether the cytotoxic and genotoxic effects of flavonoids can trigger cancer cell death, it was investigated the activity of hesperidin on DU145 prostate cancer cells. The study revealed that hesperidin influenced cancer cell count and proliferation, enhanced intracellular ROS and superoxide production, and induced DNA double-strand breaks and micronuclei formation. Genotoxicity observed in DU145 cells led to pro-apoptotic activity. Additionally, as a DNA hypomethylating agent, hesperidin was found to influence the epigenetic landscape, altering gene expression patterns. In a separate study, (Fernández-Bedmar *et al.,* 2017) examined the methylation patterns induced by hesperidin using the HL60 cell line to explore its chemopreventive potential in epigenetic cancer therapy. Their findings were further validated through an in vivo pilot study using a rat model of diethylnitrosamine-induced hepatocarcinogenesis. The reversal of hypermethylation of RARβ2 gene by *Withania somnifera* extract in a cervical cancer cell line (Jha *et al.,* 2014). The hesperidin well demonstrated cytotoxic effects and significantly hypomethylated LINE-1 and ALUM2 sequences without affecting the body or liver weight of the rats while reducing induced liver nodules. These findings suggest hesperidin as a promising candidate for chemoprevention in epigenetic therapy applications.

Naringenin

Naringenin is a widely distributed flavonoid commonly found in plants, particularly abundant in citrus fruits such as oranges, mandarins, and grapefruits. Extensive research has highlighted its diverse pharmacological properties, including antioxidant, anti-diabetic, and anti-inflammatory effects. Notably, naringenin exhibits potent anticancer activity by promoting apoptosis and inducing cell cycle arrest in various cancer cell lines, such as MDA-MB-231, HepG2, E0771, PC3, and LNCaP. Additionally, it plays a crucial role as an anti-angiogenic chemopreventive agent. Yan *et al.* (2016) demonstrated its protective effects on kidney function and its regulatory influence on the let-7a/TGFBR1 signaling pathway in diabetic nephropathy models, including both diabetic nephropathy rats and mesangial cells exposed to high glucose levels. Their findings indicated that the let-7a pathway, through its involvement in the TGF-β1/Smad signaling cascade, formed a negative feedback loop that inhibited ECM deposition by targeting TGFBR1, suggesting that naringenin may suppress glomerular mesangial cell proliferation and ECM buildup through this pathway, with let-7a emerging as a potential therapeutic target for diabetic nephropathy. Furthermore, Curti *et al.* (2017) explored naringenin's role in modulating the expression levels of miR-17-3p, miR-25-5p, and their corresponding mRNA targets associated with antioxidant and anti-inflammatory functions. Their PCR-based studies on Caco-2 cells revealed that naringenin's antioxidant properties may be mediated through epigenetic regulation by downregulating miR-17-3p and miR-25-5p.

Flavanonols

One of the least explored classes of flavonoids is those containing a flavan-3-one core, characterized by a 2-phenyl-3,4-dihydro-2H-1-benzopyran structure with a hydroxyl group at carbon C2 and a ketone group at carbon C3. The anticancer and epigenetic potential of this group has been primarily evaluated through a representative molecule, taxifolin.

Taxifolin

Taxifolin, a naturally occurring flavonoid found in various plant sources, exhibits potent anticancer properties. Beyond its known ability to modulate antioxidant pathways and inflammatory responses, taxifolin exerts its anticancer effects mainly through epigenetic mechanisms. By

inhibiting DNA methyltransferases and histone deacetylases, taxifolin promotes the demethylation of the Nrf2 gene promoter and increases histone acetylation, leading to enhanced Nrf2 expression. This upregulation of Nrf2, a key transcription factor involved in cellular defense, effectively suppresses cancer cell growth. These findings underscore the significance of epigenetic modulation in taxifolin's anticancer activity and highlight its potential as a promising therapeutic agent for cancer prevention and treatment (Kuang *et al.,* 2017).

Flavones

Flavones, a prominent class of flavonoids, possess a distinctive 2-phenyl-1-benzopyran-4-one core structure. While abundantly found in various herbs, such as parsley and celery, flavones are uniquely ubiquitous within the cereal grain family. Indeed, they represent the sole flavonoid class detectable in virtually all edible cereal species, encompassing maize, wheat, rye, barley, oats, sorghum, and millets. This widespread presence of flavones within our staple food sources is particularly noteworthy, as certain structural features within these compounds, such as the critical C2–C3 double bond, have been strongly correlated with enhanced biological activities. These structural features significantly contribute to their potent preventative effects against a range of diseases, particularly those linked to inflammation and the development of cancer (Bouyahya *et al.*, 2022).

3,6-dihydroxyflavone (3,6-DHF)

It demonstrates potent anticancer activity in breast cancer by intricately modulating epigenetic mechanisms. By inhibiting DNA methyltransferase 1, 3,6-DHF reduces DNA methylation at the miR-34a promoter, leading to increased miR-34a expression. Concurrently, 3,6-DHF alters histone modifications, such as reducing histone acetylation at the miR-21 promoter, consequently downregulating miR-21. This orchestrated regulation of microRNAs by 3,6-DHF effectively suppresses the PI3K/Akt/mTOR signaling pathway, a crucial driver of breast cancer cell growth and survival. These findings underscore the significance of epigenetic modulation in the anticancer effects of 3,6-DHF and position it as a promising therapeutic agent for breast cancer treatment (Balasubramanian *et al.*, 2019).

Apigenin

Apigenin, a naturally occurring flavonoid, exhibits potent anticancer properties by modulating epigenetic mechanisms. It inhibits enzymes that regulate DNA and histone methylation, leading to changes in gene expression (Bouyahya *et al.*, 2022). In prostate cancer cells, apigenin inhibits histone deacetylases, promoting histone acetylation, which upregulates tumor suppressor genes like p21, ultimately leading to cell cycle arrest and apoptosis. In breast cancer cells, apigenin induces cell cycle arrest by regulating key cell cycle proteins and increasing p21 expression through histone acetylation at its promoter. These findings highlight the significant role of epigenetic modulation in apigenin's anticancer effects (Ali *et al.*, 2017).

Baicalein

Baicalein, a flavonoid naturally occurring in various plants including *Scutellaria* species and Indian trumpet flower, possesses a range of several biological activities, including anti-inflammatory properties and the ability to inhibit smooth muscle cell growth. While baicalein exhibits anti-cancer effects in MCF7 breast cancer cells, studies have not provided strong evidence to support its role as a direct epigenetic modulator. Although baicalein inhibits the activity of DNA methyltransferases, crucial enzymes for DNA methylation, it does not significantly alter the methylation patterns of key tumor suppressor genes or the overall methylation status of histone H3. These findings suggest that while baicalein demonstrates anti-cancer properties, its primary mechanism of action in MCF7 cells may not involve direct epigenetic modulation (Forzato *et al.*, 2020).

Casticin

Casticin, a naturally occurring flavonoid derived from diverse plant sources, has demonstrated promising anticancer activity. In gastric cancer cells, casticin enhances RECK (Reversion-inducing cysteine-rich protein with Kazal-like domains) expression, a key regulator of tissue breakdown, by decreasing methylation of the RECK gene promoter, suggesting an epigenetic mode of action. Concurrently, casticin diminishes DNMT1 (DNA methyltransferase 1)

expression, an enzyme critical for DNA methylation. These findings collectively suggest casticin's ability to suppress gastric cancer cell proliferation through epigenetic mechanisms. In hepatocellular carcinoma (HCC) cells, casticin selectively inhibits cell growth while sparing normal liver cells. Mechanistically, casticin suppresses DNMT1 activity and expression, increasing miR-148a-3p, a microRNA that negatively regulates DNMT1. This intricate interplay between DNMT1 and miR-148a-3p highlights a potential mechanism through which casticin exerts its anti-cancer effects in HCC, likely by influencing the stem cell-like properties of these cancer cells (Azizul *et al.*, 2021). Further natural compounds are discussed in table1.

Table 1: Classification of Natural compounds, their sources, and biological activities.

Class	Compounds	Natural sources	Mechanism of action	Biomedical applications	References
Alkaloids	Morphine	Opium poppy (*Papaver somniferum*)	Binds to opioid receptors, blocks pain transmission	Pain relief, analgesic	Newman and Cragg (2020)
	Vinblastine	Madagascar periwinkle (*Catharanthus roseus*)	Inhibits microtubule assembly, disrupts mitosis	Anticancer (lymphomas, leukemia)	
	Berberine	Barberry (*Berberis vulgaris*)	Modulates AMPK pathway, inhibits DNA topoisomerases	Antidiabetic, antimicrobial, anticancer	
Flavonoids	Quercetin	Apples, onions, berries	Scavenges free radicals, modulates signaling pathways	Antioxidant, anti-inflammatory	Williams *et al*. (2021)
	Catechins (EGCG)	Greentea (*Camellia sinensis*)	Inhibits tumor growth, reduces oxidative stress	Anticancer, cardioprotective	
Terpenoids	Paclitaxel (Taxol)	Pacific yew tree (*Taxus brevifolia*)	Stabilizes microtubules, prevents cell division	Anticancer (breast, ovarian cancer)	Cragg and Newman (2013)
	Artemisinin	Sweet wormwood (*Artemisia annua*)	Generates free radicals in malaria parasite cells	Antimalarial, anticancer	
	Betulinic acid	Birch tree (*Betula species*)	Induces apoptosis via mitochondrial pathway	Antitumor, antiviral, anti-inflammatory	
Phenolics	Curcumin	Turmeric (*Curcuma longa*)	Suppresses NF-$\varkappa$B signaling, inhibits inflammatory cytokines	Anticancer, anti-inflammatory	Gupta *et al*. (2022)
	Resveratrol	Grapes, red wine	Activates sirtuins, modulates apoptosis and autophagy	Cardioprotective, neuroprotective	
Saponins	Diosgenin	Wild yam (*Dioscorea villosa*)	Modulates steroidogenesis, induces apoptosis in cancer cells	Hormone precursor, anticancer	
	Ginsenosides	Ginseng (*Panax ginseng*)	Modulates immune function, inhibits tumor growth	Adaptogenic, immuno-modulatory, anticancer	
Carotenoids	Beta-carotene	Carrots, sweet potatoes	Precursor of vitamin A, enhances immune function	Vision health, antioxidant	Maiani *et al*. (2009)
	Lycopene	Tomatoes, watermelon	Scavenges reactive oxygen species, inhibits cancer cell proliferation	Anticancer (prostate, lung)	
Polyphenols	Ellagic acid	Pomegranate, strawberries	Inhibits DNA damage,	Antioxidant, anticancer	Kumar and Pandey (2013)
Sulfur Compounds	Allicin	Garlic (*Allium sativum*)	Disrupts bacterial and fungal cell membranes	Antimicrobial, cardiovascular health	Traka and Mithen (2009)
	Sulforaphane	Broccoli, Brussels sprouts	Activates Nrf2 pathway, induces detoxifying enzymes	Chemopreventive, detoxifying	
Coumarins	Scopoletin	Tonka beans, citrus fruits	Modulates, inflammation, inhibits platelet aggregation	Anticoagulant, antioxidant	Venugopala *et al*. (2013)
	Aesculetin	Horse chestnut (*Aesculus hippocastanum*)	Inhibits oxidative stress	Vasoprotective, anti-inflammatory	
Lignans	Secoisolariciresinol	Flaxseeds, sesame seeds	Acts as phytoestrogen, modulates hormone metabolism	Breast cancer prevention, antioxidant	Adlercreutz (2007)
	Podophyllotoxin	Mayapple (*Podophyllum peltatum*)	Inhibits topoisomerase II, prevents DNA replication	Anticancer, antiviral	

BIOACTIVE AVAILABILITY

Research has demonstrated the biological activity of phytonutrients and their protective role in the molecular mechanisms underlying certain human diseases, including cancer, using diverse experimental models. A key obstacle to their effective use is their low bioavailability and bioaccessibility. Bioavailability describes the number of bioactive molecules that successfully traverse the digestive tract, are absorbed, and reach their target tissues (either intact or metabolized) to exert their biological effects or be stored. Bioaccessibility, on the other hand, refers to the proportion of a consumed compound liberated from the food matrix during digestion, making it available for absorption in the small intestine and potentially subject to transformation by the gut microbiota. Bioactivity represents the activity of the absorbed compounds, or their metabolic products, at the cellular level, resulting in biological effects within the organism (Kan *et al.*, 2022).

The study of polyphenol and other bioactive compound bioavailability is gaining importance in the development of nutraceutical products. Factors such as molecular structure, water solubility, and the composition of the food matrix influence bioaccessibility and digestibility. Additionally, membrane transporters and metabolizing enzymes play a role in modulating the bioefficacy of phytonutrients. Technological processes, cooking, and heat treatments can also affect bioavailability, and post-absorption plasma levels of many phytonutrients tend to be low. Individual variability in response can also impact phytonutrient bioavailability and bioactivity. The gut microbiota is known to biotransform polyphenols and other bioactive molecules in the large intestine. Advances have been made in enhancing the bioavailability of some compounds. Current research is exploring novel delivery strategies, including lipid carriers, nano-emulsions, molecular enhancers, and encapsulation systems. Various delivery systems have been developed for both carotenoids and polyphenols. Nevertheless, further investigation is required. Ultimately, the health benefits of dietary phytonutrients must be substantiated in well-controlled human trials using appropriate dosages (Zheng *et al.*, 2022).

CONCLUSION AND FUTURE PERSPECTIVE

This work investigated the role of epigenetic pathways in the initiation and progression of carcinogenesis. The review detailed how diverse epigenetic regulatory mechanisms can contribute to genomic instability and neoplastic transformation. These epigenetic regulators are essential for the maintenance of cellular identity, and perturbations within these pathways can result in the loss of this cellular memory, predisposing normal cells to malignant conversion. Critically, epigenetic modifications are reversible, offering a great potential for the therapeutic intervention through proper pharmacological modulation.

This review demonstrated that natural products, notably flavonoids and phenolic acids, can exert modulatory effects on key epigenetic modifiers, including DNA methyltransferases (DNMTs), histone deacetylases (HDACs), and histone methyltransferases (HMTs). These 'epi-drugs' have shown promising anticancer activity in both *in vitro* and *in vivo* models. While the pharmacodynamic profiles of these anticancer epi-drugs, specifically their interactions with their respective epigenetic targets, have demonstrated target specificity, a more comprehensive understanding of their pharmacokinetic properties-including absorption, distribution, metabolism, and excretion (ADME)- is required to fully elucidate their bioavailability and metabolic fate. Furthermore, rigorous evaluation of the toxicological profile of these epi-drugs is paramount to establish their safety for clinical application. This study suggests that the clinical translation of natural epi-drugs holds considerable promise for the discovery of novel bioactive compounds with targeted epigenetic mechanisms of action for chemotherapeutic applications. Select molecules may also have utility in targeted chemoprevention strategies.

ACKNOWLEDGMENT

The author acknowledges the help provided by the School of Biosciences and Technology, Galgotias University, Greater Noida, India.

REFERENCES

1. **Adlercreutz H.** (2007). Lignans and human health. *Critical Reviews in Clinical Laboratory*

Sciences. 44(5-6): 483-525. https://doi.org/10.1080/10408360701612942

2. **Agarwal N. and Jha A.K.** (2025). DNA hypermethylation of tumor suppressor genes among oral squamous cell carcinoma patients: a prominent diagnostic biomarker. *Molecular Biology Reports*. 52(1): 1-13. https://doi.org/10.1007/s11033-024-10144-0
3. **Ali F., Rahul Naz F., Jyoti S. and Siddique Y.H.** (2017). Health functionality of apigenin: A review. *International Journal of Food Properties*. 20(6): 1197-1238. https://doi.org/10.1080/10942912.2016.1207188
4. **Avgerinos K.I., Spyrou N., Mantzoros C.S. and Dalamaga M.** (2019). Obesity and cancer risk: Emerging biological mechanisms and perspectives. *Metabolism*. 92: 121-135. https://doi.org/10.1016/j.metabol.2018.11.001
5. **Azizul N.H., Ahmad W.A.N.W., Rosli N.L., Azmi M.A.H.M., Liang C.E., Mazlan N.W. and Assaw S.** (2021). The coastal medicinal plant *Vitex rotundifolia*: A mini-review on its bioactive compounds and pharmacological activity. *Traditional Medicine Research*. 6(2):11. https://doi.org/10.12032/TMR20201128209
6. **Baig M.H., Adil M., Khan R., Dhadi S., Ahmad K., Rabbani G. *et al.*** (2019). Enzyme targeting strategies for prevention and treatment of cancer: Implications for cancer therapy. *Seminars in Cancer Biology*. 56: 1-11. https://doi.org/10.1016/j.semcancer.2017.12.003
7. **Balasubramanian P.K., Kim J., Son K., Durai P. and Kim Y.** (2019). 3, 6 Dihydroxyflavone: A potent inhibitor with anti inflammatory activity targeting toll like receptor 2. *Bulletin of the Korean Chemical Society*. 40(1): 51-55. https://doi.org/10.1002/bkcs.11644
8. **Belwal T., Singh G., Jeandet P., Pandey A., Giri L., Ramola S. *et al.*** (2020). Anthocyanins, multi-functional natural products of industrial relevance: Recent biotechnological advances. *Biotechnology Advances*. 43: 107600. https://doi.org/10.1016/j.biotechadv.2020.107600
9. **Bonesi M., Loizzo M.R., Menichini F. and Tundis R.** (2018). Flavonoids in treating psoriasis. In Immunity and inflammation in health and disease (pp. 281-294). Academic Press. https://doi.org/10.1016/B978-0-12-805417-8.00023-8
10. **Bonetti F., Brombo G. and Zuliani G.** (2017). Nootropics, functional foods, and dietary patterns for prevention of cognitive decline. In Nutrition and functional foods for healthy aging (pp. 211-232). Academic Press. https://doi.org/10.1016/B978-0-12-805376-8.00019-8
11. **Bouyahya, A. Mechchate H., Oumeslakht L., Zeouk I., Aboulaghras S., Balahbib A. *et al.*** (2022). The role of epigenetic modifications in human cancers and the use of natural compounds as epidrugs: Mechanistic pathways and pharmacodynamic actions. *Biomolecules*. 12(3): 367. https://doi.org/10.3390/biom12030367
12. **Cragg G.M. and Newman D.J.** (2013). Natural products: A continuing source of novel drug leads. *Biochimica et Biophysica Acta (BBA)-General Subjects*. 1830(6): 3670-3695. https://doi.org/10.1016/j.bbagen.2013.02.008
13. **Curti V., Di Lorenzo A., Rossi D., Martino E., Capelli E., Collina S. and Daglia M.** (2017). Enantioselective modulatory effects of naringenin enantiomers on the expression levels of miR-17-3p involved in endogenous antioxidant defenses. *Nutrients*. 9(3): 215. https://doi.org/10.3390/nu9030215
14. **Dormán G., Flachner B., Hajdú I. and András C.D.** (2016). Target identification and polypharmacology of nutraceuticals. *In Nutraceuticals* (pp. 263-286). Academic Press. https://doi.org/10.1016/B978-0-12-802147-7.00021-8
15. **Farheen, Shreya K.S., Mathur R. and Jha A.K.** (2025). Natural compounds as epigenetic modulators: Reversing DNA hyper-methylation in cancer. *World Academy of Sciences Journal*. 7(2):20. https://doi.org/10.3892/wasj.2024.308
16. **Fernández Bedmar Z., Anter J., Alonso Moraga A., Martín de las Mulas J.,**

Millán Ruiz Y. and Guil-Luna S. (2017). Demethylating and antihepato-carcinogenic potential of hesperidin, a natural polyphenol of Citrus juices. *Molecular Carcinogenesis*. 56(6): 1653-1662. https://doi.org/10.1002/mc.22621

17. **Forzato C., Vida V. and Berti F.** (2020). Biosensors and sensing systems for rapid analysis of phenolic compounds from plants: a comprehensive review. *Biosensors*. 10(9): 105. https://doi.org/10.3390/bios10090105
18. **Gupta S.C., Patchva S. and Aggarwal B.B.** (2022). Therapeutic roles of curcumin: lessons learned from clinical trials. *The AAPS Journal*. 15(1): 195-218. https://doi.org/10.1208/s12248-012-9432-8
19. **Hermawan A., Putri H. and Utomo R.Y.** (2020). Comprehensive bioinformatics study reveals targets and molecular mechanism of hesperetin in overcoming breast cancer chemoresistance. *Molecular Diversity*. 24: 933-947. https://doi.org/10.1007/s11030-019-10003-2
20. **Jha A.K., Mohsen Nikbakht M.N., Neena Capalash N.C. and Jagdeep Kaur** (2014). Demethylation of RAR β 2 gene promoter by *Withania somnifera* in HeLa cell line. *European Journal of Medicinal Plants.* 4(5): 503-510.
21. **Jha A.K., Sharma V., Nikbakht M., Jain V., Sehgal A., Capalas N. and Kaur J.** (2016). A comparative analysis of methylation status of tumor suppressor genes in paired biopsy and serum samples from cervical cancer patients among North Indian population. *Russian Journal of Genetics*. *52*: 226-230. https://doi.org/10.1134/S1022795416010075
22. **Jha M., Aggarwal R., Jha A.K. and Shrivastava A.** (2015). Natural compounds: DNA methyltransferase inhibitors in oral squamous cell carcinoma. *Applied Biochemistry and Biotechnology*. 177: 577-594. https://doi.org/10.1007/s12010-015-1768-y
23. **Kan J., Wu F., Wang F., Zheng J., Cheng J., Li Y. *et al.*** (2022). Phytonutrients: Sources, bioavailability, interaction with gut microbiota, and their impacts on human health. *Frontiers in Nutrition*. 9:960309. https://doi.org/10.3389/fnut.2022.960309
24. **Karthi N., Karthiga A., Kalaiyarasu T., Stalin A., Manju V., Singh S.K., Cyril Ravi *et al.*** (2017). Exploration of cell cycle regulation and modulation of the DNA methylation mechanism of pelargonidin: Insights from the molecular modeling approach. *Computational Biology and Chemistry*. 70: 175-185. https://doi.org/10.1016/j.compbiolchem.2017.08.002
25. **Khan M.K. and Dangles O.** (2014). A comprehensive review on flavanones, the major citrus polyphenols. *Journal of Food Composition and Analysis*. 33(1): 85-104. https://doi.org/10.1016/j.jfca.2013.11.004
26. **Khandia R. and Munjal A.** (2020). Interplay between inflammation and cancer. *Advances in Protein Chemistry and Structural Biology*. 119: 199-245. https://doi.org/10.1016/bs.apcsb.2019.09.004
27. **Kuang H., Tang Z., Zhang C., Wang Z., Li W., Yang C. *et al.*** (2017). Taxifolin activates the Nrf2 anti-oxidative stress pathway in mouse skin epidermal JB6 P+ cells through epigenetic modifications. *International Journal of Molecular Sciences*. 18(7): 1546. https://doi.org/10.3390/ijms18071546
28. **Kumar M. and Jha A.K.** (2023). Exploring the potential of dietary factors and plant extracts as chemopreventive agents in oral squamous cell carcinoma treatment. *Frontiers in Oral Health*. 4: 1246873. https://doi.org/10.3389/froh.2023.1246873
29. **Kumar N. and Pandey A.** (2013). Chemistry and biological activities of flavonoids: an overview. *The Scientific World Journal.* 2013:162750. https://doi.org/10.1155/2013/162750
30. **Kuo H.C.D., Wu R., Li S., Yang A.Y. and Kong A.N.** (2019). Anthocyanin delphinidin prevents neoplastic transformation of mouse skin JB6 P+ cells: epigenetic re-activation of Nrf2-ARE pathway. *The AAPS Journal*. 21: 1-10. https://doi.org/10.1208/s12248-019-0355-5

31. **Lan X., Han X., Li Q. and Wang J.** (2017). (−)-Epicatechin, a natural flavonoid compound, protects astrocytes against hemoglobin toxicity via Nrf2 and AP-1 signaling pathways. *Molecular Neurobiology*. 54:7898-7907. https://doi.org/10.1007/s12035-016-0271-y

32. **Lee W.J., Shim J.Y. and Zhu B.T.** (2005). Mechanisms for the inhibition of DNA methyltransferases by tea catechins and bioflavonoids. *Molecular Pharmacology*. 68(4): 1018-1030. https://doi.org/10.1124/mol.104.008367

33. **Li S., Li W., Wang C., Wu R., Yin R., Kuo H.C. *et al.*** (2019). Pelargonidin reduces the TPA induced transformation of mouse epidermal cells–potential involvement of Nrf2 promoter demethylation. *Chemico-Biological Interactions*. 309: 108701. https://doi.org/10.1016/j.cbi.2019.06.014

34. **Maiani G., Castón M.J.P., Catasta G. *et al.*** (2009). Carotenoids: Actual knowledge on food sources, intakes, stability, and bioavailability and their protective role in humans. *Molecular Nutrition & Food Research*. 53(S2): S194-S218. https://doi.org/10.1016/j.cbi.2019.06.014

35. **Masroor M.S., Parween S., Salim M. and Prajapati I.P.** (2020). A Note on Hepatitis Viruses causing Cancer in Human. *International Journal of Biological Innovations*. 2 (2): 126-128. https://doi.org/10.46505/IJBI.2020.2207

36. **Mazimba O. and Keroletswe N.** (2015). Flavans: Synthetic Strategies: A Review. *International Research Journal of Pure and Applied Chemistry*. 8 (3):112-146. https://doi.org/10.9734/IRJPAC/2015/17422

37. **Muhammad T., Ikram M., Ullah R., Rehman S.U. and Kim M.O.** (2019). Hesperetin, a citrus flavonoid, attenuates LPS-induced neuroinflammation, apoptosis and memory impairments by modulating TLR4/NF-?B. Signaling. *Nutrients*. 11(3): 648. https://doi.org/10.3390/nu11030648

38. **Multhoff G., Molls M. and Radons J.** (2012). Chronic inflammation in cancer development. *Frontiers in Immunology*. 2:98. https://doi.org/10.3389/fimmu.2011.00098

39. **Newman D.J. and Cragg G.M.** (2020). Natural Products as Sources of New Drugs over the Nearly Four Decades from 1981 to 2019. *Journal of Natural Products*. 83(3): 770-803. 10.1021/acs.jnatprod.9b01285.

40. **Nikbakht M., Jha A.K., Malekzadeh K., Askari M., Mohammadi S., Marwaha R.K., Kaul D. and Kaur J.** (2017). Aberrant promoter hypermethylation of selected apoptotic genes in childhood acute lymphoblastic leukemia among North Indian population. *Experimental Oncology*. 39(1):57-64

41. **Saclier M., Bonfanti C., Antonini S., Angelini G., Mura G., Zanaglio F. *et al.*** (2020). Nutritional intervention with cyanidin hinders the progression of muscular dystrophy. *Cell Death & Disease*. 11(2):127. https://doi.org/10.1038/s41419-020-2332-4

42. **Saha D., Vaishnav N., Ahsan Z., Rani N., Mathur R. and Jha A.K.** (2020). Reversal of hypermethylation and reactivation of Tumor Suppressor Genes due to natural compounds in Breast Cancer Cells. *International Journal of Biological Innovations*. 2 (1): 63-75. https://doi.org/10.46505/IJBI.2020.2109

43. **Schirrmacher V.** (2019). From chemotherapy to biological therapy: A review of novel concepts to reduce the side effects of systemic cancer treatment. *International Journal of Oncology*. 54(2): 407-419. https://doi.org/10.3892/ijo.2018.4661

44. **Shoaib S., Ansari M.A., Ghazwani M., Hani U., Jamous Y.F., Alali Z. *et al.*** (2023). Prospective epigenetic actions of organo-sulfur compounds against cancer: Perspectives and molecular mechanisms. *Cancers*. *15*(3): 697. https://doi.org/10.3390/cancers15030697

45. **Sibuh B.Z., Quazi S., Panday H., Parashar R., Jha N.K., Mathur R. *et al.*** (2023). The emerging role of epigenetics in metabolism and endocrinology. *Biology*. 12(2): 256. https://doi.org/10.3390/biology12020256

46. **Singh M., Kumar V., Sehrawat N., Yadav M., Chaudhary M., Upadhyay S. K. *et al.*** (2022). Current paradigms in epigenetic anticancer therapeutics and future challenges. *Seminars in Cancer Biology.* 83:422-440. https://doi.org/10.1016/j.semcancer.2021.03.013

47. **Sokolenko A.P. and Imyanitov E.N.** (2018). Molecular diagnostics in clinical oncology. *Frontiers in Molecular Biosciences*. *5*:76. https://doi.org/10.3389/fmolb.2018.00076

48. **Sung H., Ferlay J., Siegel R.L., Laversanne M., Soerjomataram I., Jemal A. and Bray F.** (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. *71*(3): 209-249. https://doi.org/10.3322/caac.21660

49. **Tabares-Guevara J.H., Lara-Guzmán O.J., Londoño-Londoño J.A., Sierra J.A. *et al.*** (2017). Natural biflavonoids modulate macrophage–oxidized LDL interaction in vitro and promote atheroprotection in vivo. *Frontiers in Immunology*. 8: 923. https://doi.org/10.3389/fimmu.2017.00923

50. **Traka M.H. and Mithen R.F.** (2009). Glucosinolates, isothiocyanates and human health. *Phytochemistry Reviews.* 8(1): 269-282. https://doi.org/10.1007/s11101-008-9103-7

51. **Venugopala K.N., Rashmi V. and Odhav B.** (2013). Review on natural coumarin lead compounds for their pharmacological activity. *BioMed Research International.* 2013: 963248. https://doi.org/10.1155/2013/963248

52. **Verma A.K.** (2017). A Handbook of Zoology. Shri Balaji Publications, Muzaffarnagar. Vol.5: 1-648 pp.

53. **Williams R.J., Spencer J.P. and Rice-Evans C.** (2021). Flavonoids: Antioxidants or signalling molecules? *Free Radical Biology and Medicine. 36*(7): 838-849. https://doi.org/10.1016/j.freeradbiomed.2004.01.001

54. **Xu X., Chang X., Li Z., Wang J., Deng P., Zhu X. *et al.*** (2015). Aberrant SOX11 promoter methylation is associated with poor prognosis in gastric cancer. *Cellular Oncology*. 38:183-194. https://doi.org/10.1007/s13402-015-0219-7

55. **Xu X., Chang X., Xu Y., Deng P., Wang J., Zhang C. *et al.*** (2020). SAMD14 promoter methylation is strongly associated with gene expression and poor prognosis in gastric cancer. *International Journal of Clinical Oncology*. 25: 1105-1114. https://doi.org/10.1007/s10147-020-01647-4

56. **Yan N., Wen L., Peng R., Li H., Liu H., Peng H. *et al.*** (2016). Naringenin ameliorated kidney injury through let 7a/TGFBR1 signaling in diabetic nephropathy. *Journal of Diabetes Research*. 2016: 8738760. https://doi.org/10.1155/2016/8738760

57. **Zhang Y., Wang X., Han L., Zhou Y. and Sun S.** (2015). Green tea polyphenol EGCG reverse cisplatin resistance of A549/DDP cell line through candidate genes demethylation. *Biomedicine & Pharmacotherapy*. 69: 285-290. https://doi.org/10.1016/j.biopha.2014.12.016

58. **Zhang Z.T., Cao X. B., Xiong N., Wang H.C., Huang J.S., Sun S.G. and Wang T.** (2010). Morin exerts neuroprotective actions in Parkinson disease models in vitro and in vivo. *Acta Pharmacologica Sinica*. 31(8): 900-906. https://doi.org/10.1038/aps.2010.77

59. **Zhaohui W., Yingli N., Hongli L., Haijing W., Xiaohua Z., Chao F., Wu L. *et al.*** (2018). Amentoflavone induces apoptosis and suppresses glycolysis in glioma cells by targeting miR-124-3p. *Neuroscience Letters*. 686: 1-9. https://doi.org/10.1016/j.neulet.2018.08.032

60. **Zheng Z., Zhang L. and Hou Xitan** (2022). Potential roles and molecular mechanisms of phytochemicals against cancer. *Food & Function*. 13(18): 9208-9225. https://doi.org/10.1039/D2FO01663J