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RESEARCH ARTICLE

# Comprehensive Review on Mechanistic Insights, Optimal Dosages, and Safety Prospective of Natural Products in Anticancer Therapeutics

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## ABSTRACT

Cancer remains a formidable global health challenge, necessitating sustained research efforts to develop innovative and efficacious therapeutic modalities. The exploration of alternative cancer therapies has gained prominence, given the adverse side effects associated with conventional treatments like chemotherapy. Natural medicines, particularly those derived from botanical sources, emerge as a potentially more viable option for cancer treatment within the confines of therapeutic and safe dosage parameters. This comprehensive review elucidates the effective mechanisms and safety profiles related to the dosage of these natural compounds. The literature under consideration spans and has been meticulously curated from reputable databases, including PubMed, Scopus, and Google Scholar. Noteworthy natural substances encompassed in this scrutiny include gossypol, curcumin, resveratrol, genistein, anthocyanin, and hispidulin. The review outlines their respective mechanisms, therapeutic dosages, and safety perspectives within the context of cancer treatment. These compounds manifest diverse anticancer effects, ranging from the induction of apoptosis and inhibition of cell proliferation to the modulation of crucial signaling pathways. These natural compounds exhibit promising anticancer potential by targeting key facets of cancer progression, notably by i) instigating apoptosis and ii) intervening in cell cycle checkpoints. However, a more strategic and nuanced investigation is imperative to fully elucidate their optimal dosages, modes of action, and potential synergies with existing cancer treatment modalities. This critical gap in our understanding underscores the necessity for further in-depth research to optimize the therapeutic potential of these plant-derived chemicals.

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# 1. Introduction

Cancer continues to be a significant contributor to illness and death on a global scale. Cancer is the second most significant factor causing mortality from non-communicable ailments, right after cardiovascular disease [1-4]. While there have been substantial improvements in the treatment and management of cancer, there are still significant gaps and opportunities for development. Many unfavorable side effects can arise with chemotherapy. Using plant-derived products in cancer treatment, known as natural therapies, can potentially mitigate the side effects associated with conventional treatments. Currently, a limited number of botanical products are being utilized to treat carcinoma [5]. Regardless of source or kind, every tumour cell exhibits the disease's characteristics, including uncontrolled proliferation, angiogenesis, and apoptosis resistance [6,7]. Significantly, when it comes to warding off cancer, apoptosis is a significant player [8,9]. In both development and programmed cell death, "apoptosis" is essential [10]. To explain the distinct way cells die, Kerr coined the term "apoptosis" in 1972. Apoptosis is characterized by morphological changes in the cell being killed, such as nuclear fragmentation and condensation, mitochondrial external membrane permeabilization, membrane blebbing, cell shrinkage, and creating an apoptotic body [11]. Death receptor-mediated apoptosis and mitochondrial-dependent apoptosis are the two basic types of apoptosis [12]. Researchers have stated that herb-based therapies are highly effective options for treating and preventing the occurrence of cancer. This is primarily due to the diverse range of bioactive compounds present in plants that exhibit anticancer properties through numerous routes. Such chemicals could be isolated and utilized independently or with other antitumor therapies. Compared to pharmaceutical medications, these natural chemicals are readily accessible, more affordable, and can generally be taken orally with few side effects. Additionally, they have a diverse range of physiologically active chemical structures [13-17].

There has been an increase in the number of preferences for utilizing natural products originating from plants. However, it is essential to recognize the potential adverse consequences of an incorrect dosage of these substances. Most medicinal plant material is obtained from wild populations, where a combination of inherent and external variables leads to a diverse generation of phytochemical compounds. The presence of varying levels of biologically active chemicals in plant material can impact the effectiveness and safety of the treatment. Furthermore, plants synthesize secondary agents to deter, incapacitate, poison, or eliminate species that threaten them. Therefore, specific

secondary metabolites that are biologically active have the potential to cause mutations, genetic damage, or cancer. The presence of pollutants from natural or human causes often compromises the quality of medieval medicines and herbal treatments. This can lead to harmful effects and, in severe cases, even death [18]. The review focuses on the significant natural compounds found in plants, namely gossypol, curcumin, resveratrol, genistein, anthocyanin, and hispidulin provided with their structure (as shown in Figure 1), their mechanism of action in treating cancer, and their safety profile regarding dosage.

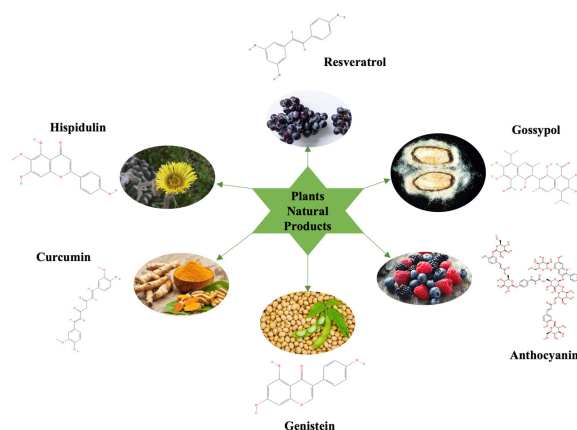


Figure 1. Selective plants base natural anti-cancer compound.

## 2. Review Methodology

We searched grey literature from January 2008 to September 2023 using PubMed, Scopus, and Google Scholar. "Plants" or "plant extracts", "secondary compounds safety profiles" from plants, and a second key phrase indicating that the article discussed an illness linked with plant use, such as "cancer", were all required for the search method to produce relevant results. The title and abstract were initially employed to demonstrate qualification. The full papers' eligibility was then determined. Universiti Terengganu Malaysia provided the articles; their entire texts are unavailable online. After selecting the titles, the abstracts of 70 papers were read. We chose the publications that would be included in the study after thoroughly reviewing each one against our inclusion and exclusion criteria list. A publication must have been published between January 1, 2008, and September 30, 2023, to be considered. Even though these articles featured studies of the past and future, no thought was given to whether they were accessible to the general audience. Grey literature was discovered by searching numerous search databases for "books", "dissertations", "working papers", or "government publications". Non-English languages are now the only ones

subject to exclusion criteria.

### 3. Cancer Statistics, Prognosis and Defective Regulatory Mechanisms

Cancer is a major global cause of mortality. Although breakthroughs have been made in the field of cancer therapy, the impact of cancer on patients persists, making it the primary cause of mortality on a global scale. Complex diseases, incredibly “aggressive” and “metastatic carcinoma”, still require treatment<sup>[19-23]</sup>. The number of new cancer episodes in the United States in 2023 will be roughly 1,958,310, averaging about 5,370 cases daily. Additionally, there will be 89,070 new instances of melanoma in situ of the skin and 55,720 new cases of intraductal carcinoma in females<sup>[24]</sup>. Carcinogenesis is a steady process in which tumours develop<sup>[25]</sup> and is characterized by specific molecular alteration<sup>[26]</sup>, the accumulation of mutations and epigenetic modifications that trigger oncogenes, the suppression of tumour suppressor genes, the impairment of DNA repair mechanisms, and the impairment of apoptosis mechanisms<sup>[25]</sup>. These modifications lead to uncontrolled cellular division<sup>[26]</sup>. Tumour genesis is an expeditious and irreversible phenomenon that commences with exposure to a carcinogenic agent, subsequently leading to its conveyance to tissues, where it induces DNA alterations. During the promotion phase, which is a prolonged and changeable process, the cells that originated the tumour undergo rapid multiplication, leading to the buildup of further genetic alterations. The ultimate phase of the development of cancer, known as advancement, occurs once these genetic changes give rise to a cellular phenotype capable of invading surrounding tissues and spreading to distant sites<sup>[26,27]</sup>. Chemotherapy is a crucial aspect of the clinical management of cancer, coupled with radiation therapy. The combined effects of these treatments are highly potent compared to using either therapy alone. However, the low bioavailability and substantial systemic toxicity of chemotherapy are its main drawbacks, which have led to the discovery of novel treatments for the management of cancer<sup>[28-31]</sup>. The escalating fascination in the quest for novel therapeutic agents fighting cancer has compelled researchers to explore inventive reservoirs of anticancer chemicals in biological sources, such as plants<sup>[16,32]</sup>. Cancer aetiology may be associated with abnormalities in dying cell mechanisms such as “autophagy”, “necrosis”, and the most appealing cell death process, “apoptosis”: “programmed cell death”, the highly regulated method of spontaneous cell death that regulates tissue formation. “Apoptosis” is a form of dying cells characterized by distinct changes in cell morphology and metabolic processes. The process involves highly controlled irrevocable events,

including phosphatidylserine externalization and DNA fragmentation, through the intrinsic and extrinsic pathways<sup>[33]</sup>.

### 4. Understanding the Safety Challenges in Natural Anti-cancer Agents

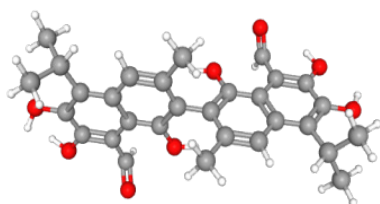
Products obtained from natural sources such as fruits and vegetables, herbaceous plants, and sea species have shown effectiveness in fighting cancer. The organic compounds are thoroughly described as having diverse tumour-fighting capabilities, such as the ability to trigger apoptosis and autophagy and suppress cell proliferation. Alkaloids, flavonoids, terpenoids, polysaccharides, and saponins are biologically active compounds that are derived from organic sources and have powerful physiological capabilities, including antitumor, analgesic, anti-inflammatory, immunomodulatory, antiviral, etc.<sup>[34]</sup>. Numerous civilizations have long utilized plant-derived cures or natural pharmaceuticals as the foundation of traditional medicine. The pharma industry has recognized the importance of medications derived from organic sources<sup>[35,36]</sup>. Many chemically and physiologically distinct compounds can be found in plants. Secondary metabolites have been extensively utilized in the therapy<sup>[37]</sup>. The National Cancer Institute (NCI) in the United States has examined over 114,000 extracts derived from 35,000 plant kinds to assess their effectiveness against various tumour types<sup>[38,39]</sup>. Notably, 70% of the existing anticancer medications on the marketplace are derived from natural ingredients or have been acquired from plants<sup>[40]</sup>. According to reports, 65% and 80% of the world’s population lives in developing nations and relies primarily on plants for their healthcare requirements<sup>[41,42]</sup>. Plant-derived phytochemicals and their derivatives offer hopeful possibilities for enhancing cancer individuals’ responses to therapy and reducing side effects. The initial step in creating an efficient and side-effect-free phytochemical-based anticancer medication is to examine organic extracts (from either wet or dry plant content) for possible antitumor biological effects. This results from separating beneficial “phytochemicals” based on “bioassay-guided fractionation” and evaluation for “*in vitro*” and “*in vivo*” responses<sup>[43]</sup>. While people commonly associate “natural” with “safe”, experts acknowledge that elements found in these natural products (NPs) can lead to toxicity<sup>[44]</sup>. Even so, mounting data suggests these natural compounds may pose safety risks<sup>[45]</sup>. Nevertheless, insufficient data supports these substances’ adverse impacts on health<sup>[46]</sup>. Various apprehensions exist concerning the safety of organic products. The intricate structure of these formulations is a cause for concern<sup>[47]</sup>. Both complex natural formulations and essential natural

medications contain numerous biologically reactive components that can potentially cause harmful consequences. Incorrect identification of medicinal plants and their usage for inappropriate therapeutic reasons are additional sources of potential concerns. Lastly, it is essential to consider the potential pharmacological interactions between natural products and chemical drugs individuals consume<sup>[48]</sup>. Various techniques have been widely utilized to assess the safety of organic products. These techniques include “*in-vitro*” and “*in-vivo*” tests for toxicity determination regarding various cells and organs<sup>[49,50]</sup>. Selective natural products and their safety profile are discussed in this review.

## 5. Natural Products, Mechanism of Action, and Safety Profile

### 5.1 Gossypol

A complex polyphenolic substance called gossypol is a substance that naturally occurs in the “glands”, “leaves”, “stems”, “roots”, and “seeds” of cotton plants<sup>[51-53]</sup>. The cotton plant seed part has the most significant amount of gossypol. The chemical formula of the compound is  $C_{30}H_{30}O_8$ , and its chemical structural formula is 2,2'-bis(8-formyl-1,6,7-trihydroxy-5-isopropyl-3-methylnaphthalene)<sup>[51,54,55]</sup>. Figure 2 depicts the 3D configuration of gossypol<sup>[56]</sup>.



**Figure 2.** 3D structure of gossypol.

#### *Mechanism of Action*

The primary targets that gossypol and its derivatives interest are Bcl-2 family proteins, which include the apoptosis inhibiting proteins “Bcl-2” and “Bcl-XL”. Gossypol analogues have a complex molecular mechanism that includes apoptosis, autophagy, cell cycle arrest, and other aberrant cellular events. Gossypol and its derivatives synergize with other chemo- and radiotherapeutic therapies and have antitumor effects on several cancer types, “*in vitro*” and “*in vivo*”<sup>[57]</sup>. Studies have shown that gossypol inhibits cancer cell invasion, motility, and angiogenesis while exerting anticancer activity via DNA damage and death<sup>[58-61]</sup>. Although the anticancer properties of gossypol have been studied in several malignancies, including lung cancer, leukaemia, and ovarian cancer, the intracellular mechanisms of these properties remain unknown<sup>[62]</sup>. Gos-

sypol affects apoptosis and anti-proliferation by various mechanisms. It has been demonstrated that gossypol ceases the development of human carcinoma of the prostate (PC-3) by increasing the secretion of the transforming growth factor  $\beta$ 1 protein (TGF $\beta$ 1). This protein acts as a negative regulator of cell growth and controls regulatory proteins of the cell cycle of “cyclin D1” and Rb functioning and expression levels. These proteins are involved in the progression of the cell cycle from the G1-phase to the S-phase in prostate cancer cells<sup>[63,64]</sup>.

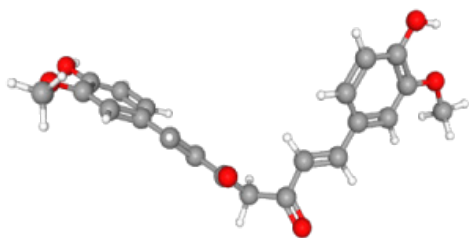
#### *Dosing and Toxicity*

Researchers conducting clinical trials on the application of orally administered gossypol/AT-101 to cancer patients have noted that it remains uncertain why certain patients show positive responses to the therapy while others do not. At a dosage of 20 mg per day, the observations were relatively mild and comprised fragility, changes in desire for food (both decrease and increase), dry mouth, and nausea<sup>[65]</sup>. The documented toxicities threshold in cancer patients can be broadly divided into hematologic, cardiac, “dermatologic”, “gastrointestinal”, “hepatic”, and metabolic events, as well as dietary behaviour and other problems (including lethargy, headaches, and sleeplessness). The prevailing haematological toxic effects described were anaemia, leukopenia, thrombocytopenia, and neutropenia<sup>[53,66-77]</sup>. Even though numerous laboratory and clinical investigations have explored the genetic effects of gossypol, there still needs to be a comprehensive approach to accurately assessing its risk of causing genetic damage. Most of the observed positive consequences are expected to be either eradicated or negligible *in vivo* at the anticipated clinical doses when normal serum protein levels are present. Alternatively, these effects can be attributed to mechanisms involving alterations in enzymes and other cellular components in DNA replication rather than direct interactions with DNA. However, due to the possible hazards of using a drug as a contraceptive before completely understanding its genetic adverse effects, it is essential to conduct further study on the direct impacts of gossypol and its methods of action in both standard and cancerous cells. This information would be valuable for assessing the safety of gossypol and discovering potential novel applications of the compound substance<sup>[78-82]</sup>.

### 5.2 Curcumin

Polyphenols are the chemical family to which “curcumin” belongs; its IUPAC name is (1E, 6E) and it’s chemically known as diferuloylmethane. 1,7-dihydroxy-4-methoxybenzene, the compound -1,6-heptadiene-3,5-dione, has a chemical formula of  $C_{21}H_{20}O_6$  and a molecular weight of 368.38 g/mol<sup>[83]</sup>. Figure 3 shows 3D structure of cur-

cumin<sup>[84]</sup>. Curcumin, an active component extracted from the rhizome of the dietary spice turmeric (*Curcuma longa*), is part of the Zingiberaceae plant group native to southern and eastern tropical Asia<sup>[85]</sup>. Curcumin has an extensive historical record of being utilized to treat various problems and metabolic illnesses, including various tumour conditions, cough, wounds on the skin, and inflammatory conditions, in addition to its colouring, taste, and preservation capabilities in food<sup>[86]</sup>. Recent research has shown that curcumin has several medicinal effects, including anti-inflammatory, antioxidant, and anticancer capabilities<sup>[87-89]</sup>.



**Figure 3.** 3D structure of curcumin.

#### **Mechanism of Action**

The primary modes of working through which curcumin demonstrates its distinct anti-carcinogenic efficacy include activating “apoptosis” and decreasing tumour proliferation and invasion by blocking a range of cellular signalling pathways<sup>[90]</sup>. Curcumin’s anticancer activity has been documented in several investigations on “breast cancer”, “lung cancer”, “head”, and “neck squamous cell carcinoma”, “prostate cancer”, and “brain tumours”<sup>[91]</sup>, demonstrating its capacity to combat numerous tumour cells<sup>[92]</sup>. As per some reports, curcumin induces apoptosis in ovarian tumour cells by a P53-independent route while acting similarly to cells with wild-type P53. Apoptosis was induced in HEY cells treated with curcumin, as evidenced by the cleavage of “poly (ADP-ribose) polymerase-1”, DNA fragmentation, nuclear fragmentation, and condensation. Apoptosis can also be induced by curcumin using both internal and extrinsic pathways. A rise in the activity of the p38 protein’s mitogen-activated protein kinases (MAPK) led to diminished antiapoptotic regulators’ survival and “Bcl-2” production. According to reports, curcumin causes specific ovarian cancer cells to undergo anticancer cell death by decreasing pro-survival Akt signalling<sup>[93,94]</sup>.

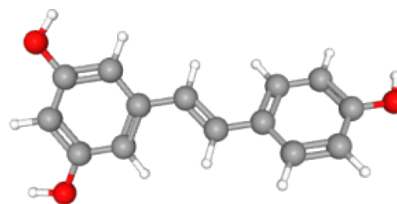
#### **Dosing and Toxicity**

Curcumin has a low toxicity profile and a safe daily consumption range of up to 3 mg/kg; side effects described by those who took 500-12,000 mg included headache, rash, and yellow stools<sup>[95]</sup>. Curcumin and its degradation products have been studied extensively in rat

models for their potential toxicity due to their interaction with and inhibition of cytochrome P450 and glutathione S-transferase, resulting in cardiotoxicity and drug-drug interactions, respectively<sup>[96]</sup>. While curcumin is effective against cancer, it has also been shown to be cytotoxic to normal human lymphocytes, kidney cells, and murine macrophage cell lines at IC<sub>50</sub> values of 15.2 μM and 31 μM, respectively<sup>[96]</sup>. It is also crucial to remember that as of November 2018, the US Food and Drug Administration designated curcumin as “Generally Recognized as Safe”, or “GRAS”. This indication covers intended usage as an ingredient in several food categories, from 0.5 to 100 mg/100 g, but not as a supplement or therapy for any health problem<sup>[97]</sup>.

### **5.3 Resveratrol**

A “polyphenolic stilbene” with two “aromatic rings” connected by an ethylene bridge is resveratrol (trans-3,5,40-trihydroxystilbene). Ring A contains two hydroxyl (OH) groups at carbons 3 and 5, while ring B contains one OH group at carbon 4’<sup>[98]</sup>. Because of its core ethylene moiety, resveratrol can exist as the cis or trans stereoisomer. It is naturally arising in trans-form (E-configuration). Trans-resveratrol photo isomerizes into a less stable and non-commercially viable cis form when exposed to UV and visible light<sup>[98-100]</sup>. Figure 4 depicts the 3D configuration of resveratrol<sup>[101]</sup>.



**Figure 4.** 3D structure of resveratrol.

#### **Mechanism of Action**

Resveratrol is considered to have antitumor characteristics because it inhibits three crucial phases of carcinogenesis: tumour start, promoting it, and advancement<sup>[102]</sup>. Resveratrol has been demonstrated to engage in several molecular targets and impaired cells associated with “breast”, “skin”, “gastric”, “colon”, “oesophageal”, “prostate”, “pancreatic cancer”, and “leukaemia”, based on *in vitro* findings<sup>[103]</sup>. Resveratrol’s ability to directly interact with cancers, including skin and gastrointestinal tract, provides the most significant evidence of its anticancer effects. Even when using extremely high doses of resveratrol, the evidence for treating other malignancies is questionable<sup>[104,105]</sup>. Cell cycle arrest and the activation of apoptotic cell death have been connected to resveratrol’s

growth-inhibitory effects in cells obtained from different origins<sup>[106-111]</sup>. The process of resveratrol-induced apoptotic cell death may involve changes in the expression of the “antiapoptotic protein Bcl-2”, impairment of “mitochondrial” function, release of “cytochrome c”, and stimulation of caspases<sup>[112-115]</sup>. In addition, studies have shown that resveratrol could trigger apoptosis (cell death) in human HCT116 colon carcinoma cells, even without p53<sup>[116]</sup>. On the other hand, p53 is necessary for resveratrol-induced apoptosis in several types of cancer cells<sup>[117-119]</sup>.

#### Dosing and Toxicity

Resveratrol is safe and well-tolerated in small amounts. However, high doses of resveratrol can be harmful<sup>[120]</sup>. Resveratrol has a weak bioavailability, which limits its medicinal use, and people are eager to use high doses of it. Toxicology studies on resveratrol have been conducted in vivo and clinical settings. It seems that resveratrol may cause nephrotoxicity at large doses—up to 3 g/kg/day in rats. Although a small number of studies have shown that resveratrol can harm the liver and increase levels of liver enzymes, such as aspartate aminotransferase, other research has suggested that it may not have any discernible liver toxicity<sup>[121,122]</sup>. Rats tolerate receiving 750 mg/kg/day of resveratrol for three months without experiencing any adverse effects<sup>[123]</sup>. Resveratrol is safe in human studies, and only a few adverse effects, such as changes in blood electrolytes, nasopharyngitis, and erythematous rash, can be seen after 400 mg of resveratrol is administered. Other frequently noted side effects of resveratrol were headache, myalgia, epididymitis, and dizziness<sup>[124-127]</sup>. Another study revealed resveratrol to be harmless and easy to digest at doses of up to 5 grams per day, either all at once or dividing up over several days' schedule<sup>[128,129]</sup>.

#### 5.4 Hispidulin

“Hispidulin (4', 5, 7-trihydroxy-6-methoxyflavone)” is a flavonol with the chemical formula  $C_{16}H_{12}O_6$  and a molecular mass of 300.26 g mol<sup>-1</sup>. Figure 5 depicts the 3D configuration of hispidulin<sup>[130]</sup>. It is predominantly found in plants belonging to the Asteraceae<sup>[131-133]</sup> and Lamiaceae families<sup>[134]</sup>. According to research, hispidulin has various biological effects, including those that are anti-inflammatory, antifungal, antiplatelet, anticonvulsant, anti-osteoporotic, and most significantly, anticancer<sup>[135,136]</sup>.

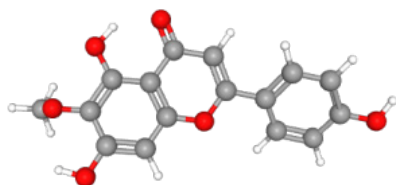


Figure 5. 3D structure of hispidulin.

#### Mechanism of Action

The “extrinsic pathway” and “intrinsic pathway” are the primary mechanisms by which hispidulin therapy in cancer cells can induce apoptosis. After inserting the BAX (pro-apoprotein) inside the “mitochondrial membrane”, “cytochrome c” is produced, resulting in the formation of an apoptosome, which subsequently commences the apoptotic cascades first by activating proapoptotic caspase 9 and then potentially, caspase 3. “Growth factors” cause a series of signalling events that finally improve the possibility of cells' need for survival by attaching to their respective receptors, which is how the mechanisms of apoptosis and hispidulin mostly function. Examples of pathways include the PI3K and AKT pathways and the JAK and STAT3 pathways. On the other hand, blocking “JAK/STAT3” and “PI3K/AKT” prevents the transcription of downstream target genes implicated in metastasis, invasion, and angiogenesis. Hispidulin inhibits mTOR and activates apoptosis via the p53 pathway<sup>[137]</sup>. A second investigation revealed that hispidulin induced apoptosis in NSCLC cells by increasing the working of cleaved “caspase-3” and cleaved “poly [ADP-ribose] polymerase”<sup>[138]</sup>.

#### Dosing and Toxicity

Hispidulin's toxicological analysis found no risk of tumorigenesis or irritation; however, there is a substantial risk to fertility<sup>[139,140]</sup>. When used at the recommended dosages, hispidulin is widely regarded as safe<sup>[135]</sup>. Additional research is needed to determine hispidulin's toxicity profile<sup>[141]</sup>.

#### 5.5 Genistein

Genistein, the most abundant isoflavone, was discovered in soy products. The compound has a chemical formula of  $C_{15}H_{10}O_5$  and a molecular weight of 270.241 g/mol<sup>[142,143]</sup>. Figure 6 depicts the 3D configuration of genistein<sup>[144]</sup>. Genistein has demonstrated preclinical efficacy towards a wide range of human tumours, including “breast”, “lung”, “liver”, “prostate”, “pancreatic”, “skin” “cervical”, “bone”, “uterine”, “colon”, “kidney”, “bladder”, “neuroblastoma”, “gastric”, “oesophagal”, “pituitary”, “salivary gland”, “testicular”, and “ovarian carcinoma”<sup>[145]</sup>.

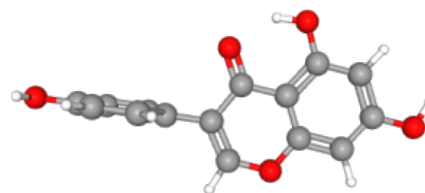


Figure 6. 3D structure of genistein.

#### Mechanism of Action

Genes closely linked to the control of programmed

cell death and the cell cycle are modulated by genistein, a promising chemopreventive drug, to decrease carcinogenesis [146,147]. Moreover, studies have demonstrated that genistein effectively hinders angiogenesis and metastasis [148,149]. These findings suggest that genistein has diverse impacts on suppressing carcinogenesis and the proliferation of cancer cells. Additionally, there might be more, yet unidentified, mechanisms by which genistein inhibits cancer [150]. Extensive research has investigated the molecular mechanism by which genistein functions as a chemotherapeutic drug in various cancer types. Genistein regulates multiple stages of the cell cycle, including programmed cell death, the formation of new blood vessels, and “metastasis”. Genistein primarily focuses on caspases, B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X protein (Bax), nuclear factor- $\kappa$ B (NF- $\kappa$ B), an inhibitor of NF- $\kappa$ B, phosphoinositide 3-kinase/Akt (PI3K/Akt), extracellular signal-regulated kinase 1/2 (ERK 1/2), mitogen-activated protein kinase (MAPK), and Wingless and integration 1/ $\beta$ -catenin (Wnt/ $\beta$ -catenin) signalling pathway at the molecular level. In addition to the transcription factors, it has been revealed that genistein-induced endoplasmic reticulum (ER) stress and its subsequent targets could also trigger apoptosis in cancer [142].

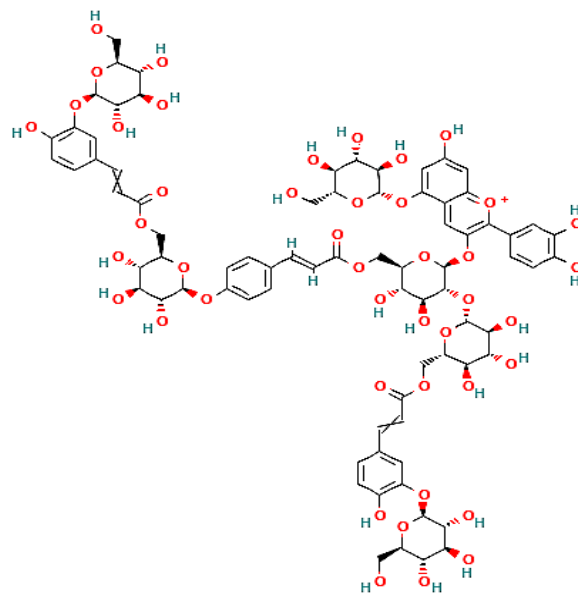
### Dosing and Toxicity

It is noteworthy that genistein use is risk-free and unlikely to have any adverse side effects, even at relatively high doses. At dosages of 16 mg/kg body weight, very few investigations have found any potential mild toxicity (clinically exhibited, such as nausea, pedal oedema, or breast soreness) [151]. When applied topically to the skin, genistein has been demonstrated to be modestly absorbed (with pH 6 buffer absorbing it the most) and to have essentially no negative effects, such as erythema or disturbance of the stratum corneum [152,153]. A study on the pharmaceutical formulation of genistein indicated that genistein HME (hot melt extrusion) was safe at doses of up to 3000 mg. There were no documented dose-limiting toxicities; most adverse reactions were mild to severe gastrointestinal problems. The maximum acceptable dose was not identified, and a dose of 500 mg was considered to have no discernible adverse effects. Genistein HME was much more bioavailable at doses of 3000 mg compared to 2000 mg [154].

## 5.6 Anthocyanin

The most prevalent flavonoids found in most plants are anthocyanins. Anthocyanins, parts of cell vacuoles, give flowers and fruit many colours, changing along with the seasons. Strawberries, grapes, apples, purple cauliflower, and maize are some foods that can display red, blue, or

violet hues [155]. Currently, there have been more than 500 varieties of anthocyanins discovered. These anthocyanins may be found in 27 plant families and 72 plant genera [156,157]. Figure 7 depicts the 2D configuration of anthocyanin [158]. Conformer creation is restricted due to an excessive number of atoms and high flexibility [158].



**Figure 7.** 2D structure of anthocyanin.

Anthocyanins have been linked to reduced apoptosis, cell development and differentiation, inflammatory reactions, and oxidative stress [159]. The impacts of anthocyanins are not solely attributed to their antioxidant capacity, which refers to their ability to neutralize and sequester radicals. Recent research has shown that anthocyanins also can modulate various molecular pathways. These pathways include those related to cytoprotection and inflammation (such as “nuclear factor erythroid 2-related factor 2”, “nuclear factor kappa-light-chain-enhancer of activated B cells”, and eNOS), metabolism (such as “phosphoinositide 3-kinases (PI3K)” and “protein kinase B (AKT), AMP-activated protein kinase (AMPK)”, and peroxisome proliferator-activated receptor gamma pathways) [160], proliferation and apoptosis (such as AMPK, MAPKs, and PI3K/AKT/mTOR pathways) as well as angiogenesis [161-165].

### Mechanism of Action

Anthocyanins can activate the production of CDK inhibitors (CDKIs), decrease the production of CDK1 and CDK2, suppress the production of cyclin B, cyclin A, and cyclin E, and induce the arrest of tumour cells in the G0/G1 and G2/M stages. Anthocyanins could suppress the proliferation of tumour cells by upregulating the expression of anti-oncogenes and diminishing the expression

of oncogenes. This effect is achieved by modulating the expression of various cyclins and their partners, CDKs, and CDKIs) <sup>[166,167]</sup>. Several papers have presented facts indicating that metabolites derived from anthocyanins have greater efficacy as anticancer drugs. The metabolites of anthocyanins effectively inhibited the proliferation of Caco2 cells <sup>[168,169]</sup>. Additionally, they have little effect on the proliferation of healthy cells and can specifically limit the growth of tumour cells <sup>[170,171]</sup>. Anthocyanins have been shown to trigger apoptosis in cancer cells via both the intrinsic mitochondrial mechanism and the extrinsic death receptor pathway. In tumour cells, “apoptosis, or programmed cell death”, is typically absent, making it impossible for dead cells to be naturally removed. Cancer cells have dysregulated multiple genes, including p53, to evade apoptosis. Consequently, these cells exhibit a much slower resistance to cell death than normal cells. Anthocyanin treatment on cancer cells leads to an elevation of mitochondrial membrane potential, accompanied by the release of cytochrome c and the regulation of caspase-dependent anti- and proapoptotic proteins in the intrinsic pathway. Anthocyanins affect the expression of “FAS” and “FASL” in the extrinsic pathway, leading to apoptosis in cancer cells <sup>[172-175]</sup>.

#### **Dosing and Toxicity**

According to analyses of anthocyanin safety and toxicology, acute toxicity is extremely low in animals, and there have been no reports of any adverse health effects in people who consume the recommended daily dose of anthocyanin. There is no suggested intake of anthocyanins for good health or to avoid side effects <sup>[176]</sup>. Although anthocyanins are not easily absorbed and quickly metabolized, frequent consumption of these compounds is considered safe. In combination with physical exercise, it is suggested that both can effectively minimize the onset of several illnesses associated with oxidative stress <sup>[177]</sup>. Currently, no recorded negative consequences have been associated with ingesting anthocyanins. Concentrating on human studies, most subjects who consumed 160 mg of anthocyanins twice a day for two months digested the extract; only 4% of the subjects disclosed adverse effects, precisely gastrointestinal issues, and eczema <sup>[177-179]</sup>.

## **6. Conclusions and Future Recommendations**

Chemotherapeutic agents in isolation exhibit limited efficacy in mitigating the adverse effects they induce and cannot selectively target signaling pathways for the comprehensive inhibition of cancer cell growth. Medicinal plants have garnered increased attention in recent years due to their myriad and distinctive anti-cancer attributes. These plants synthesize secondary metabolites that not

only selectively target cancer cells but also impede the proliferation of such cells. Noteworthy constituents, including curcumin, resveratrol, gossypol, anthocyanin, hispidulin, and genistein, have emerged from scientific scrutiny as particularly efficacious in targeting cancer cells. This determination arises from a thorough review of pertinent research and literature. The study also underscores the documented dosages of these compounds. Nevertheless, further research is imperative to comprehensively elucidate optimal dosages and the mechanistic underpinnings of these compounds concerning cancer inhibition. While these compounds may effectively target multiple cancer cells through specific modulation of signaling pathways, their administration without precise dosage determination can engender harmful toxic effects. Therefore, a nuanced understanding of dosage requirements and intricate mechanisms of action is essential to fully exploit the therapeutic potential of these plant-derived compounds in the context of cancer treatment.

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#### **Conflicts of Interest**

No conflicts of Interest.

#### **Ethics Approval**

Not applicable.

#### **Consent to Participate**

Not applicable.

#### **Consent for Publication**

All authors have consent for publication.

#### **Availability of Data and Material**

Not Applicable.

#### **Author’s Contributions**

G.S. C: Conceptualization, laying the foundation for the study’s framework, and providing the overarching vision for the research. Drafting, Editing, and Review Z.: Preparation of the initial draft, translating the conceptual ideas into a cohesive manuscript, and ensuring the articulation of critical concepts. AA: Edited and reviewed the manuscript, refined the language, and ensured the overall coherence and clarity of the content. Y.Y.S. and T.T.S. Offering valuable suggestions and insights, contributing to the refinement of the research, and enhancing the scholar-



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