Japan Bilingual Publishing Co.

Food and Drug Safety

https://ojs.bilpub.com/index.php/fds

RESEARCH ARTICLE

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

Gul-e-Saba Chaudhry[1*†] Zeenia[1†] Abdah Md Akim[2] Yeong Yik Sung[1]

Tengku Sifzizul Tengku Muhammad[1]

1. Institute of Climate Adaptation and Marine Biotechnology, Universiti Malaysia Terengganu, Kuala Terengganu, 21030, Malaysia
2. Department of Biomedical Sciences, Universiti Putra Malaysia, Seri Kembangan, Selangor, 43300, Malaysia

ARTICLE INFO

Article history
Received: 9 December 2023
Revised: 27 December 2023
Accepted: 2 January 2024
Published Online: 10 January 2024

Keywords:
Anthocyanin
Cancer
Apoptosis
Drug safety
Curcumin
Genistein gossypol
Hispidulin
Resveratrol

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.

*Corresponding Author:
Gul-e-Saba Chaudhry,
Institute of Climate Adaptation and Marine Biotechnology, Universiti Malaysia Terengganu, Kuala Terengganu, 21030, Malaysia;
Email: sababiochem@gmail.com; gul.saba@umt.edu.my
† Both contributed as first author

DOI: https://doi.org/10.55121/fds.v1i1.137

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.

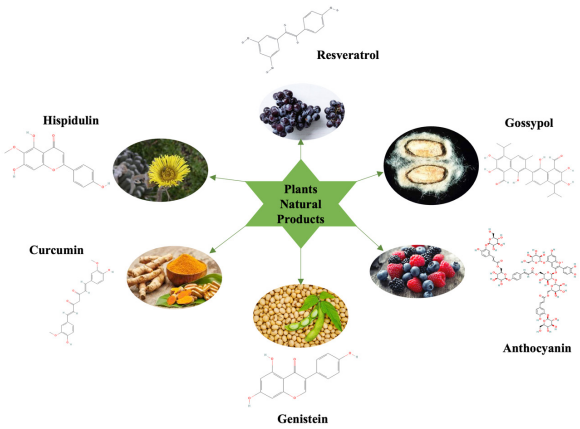

Figure 1. Selective plants base natural anti-cancer compound.

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 [19-23]. 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 [24]. Carcinogenesis is a steady process in which tumours develop [25] and is characterized by specific molecular alteration [26], 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 [25]. These modifications lead to uncontrolled cellular division [26]. 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 [26,27]. 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 [28-31]. 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 [16,32]. 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 [33].

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. [34]. 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 [35,36]. Many chemically and physiologically distinct compounds can be found in plants. Secondary metabolites have been extensively utilized in the therapy [37]. 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 [38,39]. Notably, 70% of the existing anticancer medications on the marketplace are derived from natural ingredients or have been acquired from plants [40]. According to reports, 65% and 80% of the world's population lives in developing nations and relies primarily on plants for their healthcare requirements [41,42]. 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 [43]. While people commonly associate "natural" with "safe", experts acknowledge that elements found in these natural products (NPs) can lead to toxicity [44]. Even so, mounting data suggests these natural compounds may pose safety risks [45]. Nevertheless, insufficient data supports these substances' adverse impacts on health [46]. Various apprehensions exist concerning the safety of organic products. The intricate structure of these formulations is a cause for concern [47]. 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 [48]. 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 [49,50]. Selective natural produces and their safety profile are discussed in this review.

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

5.1 Gosspyol

A complex polyphenolic substance called gossypol is a substance that naturally occurs in the "glands", "leaves", "stems", "roots", and "seeds" of cotton plants [51-53]. 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) [51,54,55]. Figure 2 depicts the 3D configuration of gossypol [56].

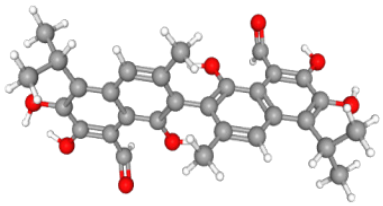

Figure 2. 3D structure of gossypol.

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*" [57]. Studies have shown that gossypol inhibits cancer cell invasion, motility, and angiogenesis while exerting anticancer activity via DNA damage and death [58-61]. 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 [62]. Gossypol 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 β1 protein (TGFβ1). 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 [63,64].

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 [65]. 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 [53,66-77]. 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 [78-82].

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 [83]. Figure 3 shows 3D structure of cur-

cumin [84]. 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 [85]. 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 [86]. Recent research has shown that curcumin has several medicinal effects, including anti-inflammatory, antioxidant, and anticancer capabilities [87-89].

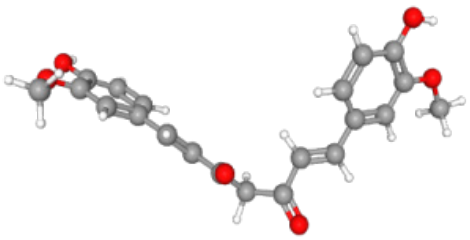

Figure 3. 3D structure of curcumin.

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 [90]. 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" [91], demonstrating its capacity to combat numerous tumour cells [92]. 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 [93,94].

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 [95]. 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 [96]. 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_{50} values of 15.2 μM and 31 μM, respectively [96]. 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 [97].

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' [98]. 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 [98-100]. Figure 4 depicts the 3D configuration of resveratrol [101].

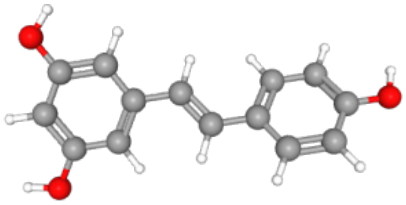

Figure 4. 3D structure of resveratrol.

Mechanism of Action

Resveratrol is considered to have antitumor characteristics because it inhibits three crucial phases of carcinogenesis: tumour start, promoting it, and advancement [102]. Resveratrol has been demonstrated to engage in several molecular targets and impaired cells associated with "breast", "skin", "gastric", "colon", "oesophagal", "prostate", "pancreatic cancer", and "leukaemia", based on *in vitro* findings [103]. 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 [104,105]. 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 [106-111]. 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 [112-115]. In addition, studies have shown that resveratrol could trigger apoptosis (cell death) in human HCT116 colon carcinoma cells, even without p53 [116]. On the other hand, p53 is necessary for resveratrol-induced apoptosis in several types of cancer cells [117-119].

Dosing and Toxicity

Resveratrol is safe and well-tolerated in small amounts. However, high doses of resveratrol can be harmful [120]. 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 [121,122]. Rats tolerate receiving 750 mg/kg/day of resveratrol for three months without experiencing any adverse effects [123]. 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 [124-127]. 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 [128,129].

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 mol1. Figure 5 depicts the 3D configuration of hispidulin [130]. It is predominantly found in plants belonging to the Asteraceae [131-133] and Lamiaceae families [134]. According to research, hispidulin has various biological effects, including those that are anti-inflammatory, antifungal, antiplatelet, anticonvulsant, anti-osteoporotic, and most significantly, anticancer [135,136].

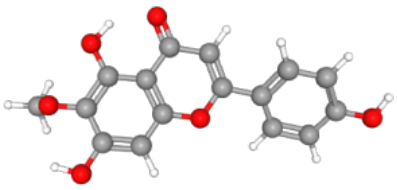

Figure 5. 3D structure of hispidulin.

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 [137]. 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" [138].

Dosing and Toxicity

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

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 [142,143]. Figure 6 depicts the 3D configuration of genistein [144]. 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" [145].

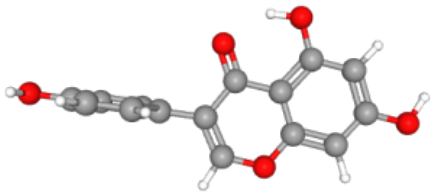

Figure 6. 3D structure of genistein.

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-κB (NF-κB), an inhibitor of NF-κB, 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/β-catenin (Wnt/β-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].

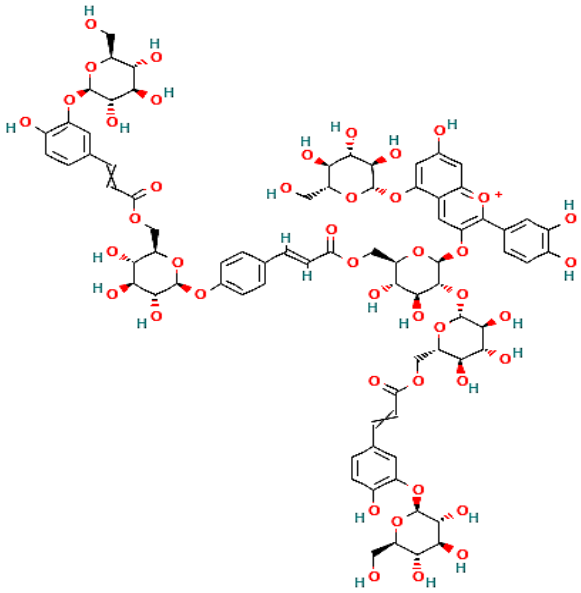

Figure 7. 2D structure of anthocyanin.

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) [166,167]. 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 [168,169]. Additionally, they have little effect on the proliferation of healthy cells and can specifically limit the growth of tumour cells [170,171]. 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 [172-175].

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 [176]. 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 [177]. 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 [177-179].

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.

Funding

No funding available for this study.

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-

ly quality of the work through their constructive input.

Acknowledgement

The authors express their gratitude to "CUSABIO" for the Biology Award, a source of inspiration and financial aid. This prestigious acknowledgment further solidifies our dedication to achieving excellence and fostering innovation in pushing the boundaries of biological fundamentals and research.

References

[1] World Health Organization, Public Health Agency of Canada, 2005. Preventing chronic diseases: A vital investment. World Health Organization: Geneva.

[2] Mathers, C.D., Loncar, D., 2006. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Medicine. 3(11), e442. DOI: https://doi.org/10.1371/journal.pmed.0030442

[3] Lopez, A.D., Mathers, C.D., Ezzati, M., et al., 2006. Global and regional burden of disease and risk factors, 2001: Systematic analysis of population health data. The Lancet. 367(9524), 1747-1757. DOI: https://doi.org/10.1016/S0140-6736(06)68770-9

[4] Deaths: Final Data for 2003 [Internet]. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/nchs/data/hestat/finaldeaths03/finaldeaths03.htm

[5] Desai, A.G., Qazi, G.N., Ganju, R.K., et al., 2008. Medicinal plants and cancer chemoprevention. Current Drug Metabolism. 9(7), 581-591. DOI: https://doi.org/10.2174/138920008785821657

[6] Arbiser, J.L., Bonner, M.Y., Gilbert, L.C., 2017. Targeting the duality of cancer. NPJ Precision Oncology. 1(1), 23. DOI: https://doi.org/10.1038/s41698-017-0026-x

[7] Xu, W., Jing, L., Wang, Q., et al., 2015. Bax-PGAM5L-Drp1 complex is required for intrinsic apoptosis execution. Oncotarget. 6(30), 30017. DOI: https://doi.org/10.18632/oncotarget.5013

[8] Lopez, J., Tait, S.W.G., 2015. Mitochondrial apoptosis: Killing cancer using the enemy within. British Journal of Cancer. 112(6), 957-962. DOI: https://doi.org/10.1038/bjc.2015.85

[9] Pfeffer, C.M., Singh, A.T., 2018. Apoptosis: A target for anticancer therapy. International Journal of Molecular Sciences. 19(2), 448. DOI: https://doi.org/10.3390/ijms19020448

[10] Peng, W., Wu, J.G., Jiang, Y.B., et al., 2015. Antitumor activity of 4-O-(2"-O-acetyl-6"-O-p-coumaroyl-β-D-glucopyranosyl)-p-coumaric acid against lung cancers via mitochondrial-mediated apoptosis. Chemico-biological Interactions. 233, 8-13. DOI: https://doi.org/10.1016/j.cbi.2015.03.014

[11] Khalil, A.M., 2021. Apoptosis, guardian of the genome. World Journal of Biology Pharmacy and Health Sciences. 5(1), 37-54. DOI: https://doi.org/10.30574/wjbphs.2021.5.1.0003

[12] Li, M., Tang, D., Yang, T., et al., 2022. Apoptosis triggering, an important way for natural products from herbal medicines to treat pancreatic cancers. Frontiers in Pharmacology. 12, 796300. DOI: https://doi.org/10.3389/fphar.2021.796300

[13] Ahmad, R., Ahmad, N., Naqvi, A.A., et al., 2017. Role of traditional Islamic and Arabic plants in cancer therapy. Journal of Traditional and Complementary Medicine. 7(2), 195-204. DOI: https://doi.org/10.1016/j.jtcme.2016.05.002

[14] Zaid, H., Silbermann, M., Ben-Arye, E., et al., 2012. Greco-Arab and Islamic herbal-derived anticancer modalities: From tradition to molecular mechanisms. Evidence-Based Complementary and Alternative Medicine. 349040. DOI: https://doi.org/10.1155/2012/349040

[15] Seca, A.M., Pinto, D.C., 2018. Plant secondary metabolites as anticancer agents: Successes in clinical trials and therapeutic application. International Journal of Molecular Sciences. 19(1), 263. DOI: https://doi.org/10.3390/ijms19010263

[16] Lichota, A., Gwozdzinski, K., 2018. Anticancer activity of natural compounds from plant and marine environment. International Journal of Molecular Sciences. 19(11), 3533. DOI: https://doi.org/10.3390/ijms19113533

[17] Hassan, B., 2020. Plants and cancer treatment. Medicinal plants: Use in prevention and treatment of diseases. Intech Open: London.

DOI: https://doi.org/10.5772/intechopen.90568

[18] van Wyk, A.S., Prinsloo, G., 2020. Health, safety and quality concerns of plant-based traditional medicines and herbal remedies. South African Journal of Botany. 133, 54-62.
DOI: https://doi.org/10.1016/j.sajb.2020.06.031

[19] Akim, A., Zafar, M.N., Abdullah, M.A., et al., 2020. Induction of apoptosis and role of paclitaxel-loaded hyaluronic acid-crosslinked nanoparticles in the regulation of AKT and RhoA. Journal of Advanced Pharmaceutical Technology & Research. 11(3), 101-106.

[20] Jan, R., Zafar, M.N., Mohammad, H., et al., 2019. Vitex rotundifolia fractions induced apoptosis in human breast cancer T-47D cell line via activation of extrinsic and intrinsic pathway. Asian Pacific Journal of Cancer Prevention. 20(12), 3555.
DOI: https://doi.org/10.31557/APJCP.2019.20.12.3555

[21] Nithya, M., Ambikapathy, V., Panneerselvam, A., et al., 2014. Anti-tumour activity of different extracts of Ganoderma lucidum (curt.: fr.) p. karst. World Journal of Pharmaceutical Research. 3(4), 2204-2214.

[22] Mou, X., Kesari, S., Wen, P.Y., et al., 2011. Crude drugs as anticancer agents. International Journal of Clinical and Experimental Medicine. 4(1), 17-25.

[23] Chaudhry, G.E.S., Sohimi, N.K.A., Mohamad, H., et al., 2021. Xylocarpus moluccensis induces cytotoxicity in human hepatocellular carcinoma HepG2 cell line via activation of the extrinsic pathway. Asian Pacific Journal of Cancer Prevention. 22(S1), 17-24.
DOI: https://doi.org/10.31557/APJCP.2021.22.S1.17

[24] Siegel, R.L., Miller, K.D., Wagle, N.S., et al., 2023. Cancer statistics, 2023. CA: A Cancer Journal for Clinicians. 73(1), 17-48.
DOI: https://doi.org/10.3322/caac.21763

[25] de Melo, F.H.M., Oliveira, J.S., Sartorelli, V.O.B., et al., 2018. Cancer chemoprevention: Classic and epigenetic mechanisms inhibiting tumorigenesis. What have we learned so far?. Frontiers in Oncology. 8, 644.
DOI: https://doi.org/10.3389/fonc.2018.00644

[26] Kotecha, R., Takami, A., Espinoza, J.L., 2016. Dietary phytochemicals and cancer chemoprevention: A review of the clinical evidence. Oncotarget. 7, 52517-52529.
DOI: https://doi.org/10.18632/oncotarget.9593

[27] Dehelean, C.A., Marcovici, I., Soica, C., et al., 2021. Plant-derived anticancer compounds as new perspectives in drug discovery and alternative therapy. Molecules. 26(4), 1109.
DOI: https://doi.org/10.3390/molecules26041109

[28] Senapati, S., Mahanta, A.K., Kumar, S., et al., 2018. Controlled drug delivery vehicles for cancer treatment and their performance. Signal Transduction and Targeted Therapy. 3, 7.
DOI: https://doi.org/10.1038/s41392-017-0004-3

[29] Hasumi, K., Aoki, Y., Watanabe, R., et al., 2011. Therapeutic response in patients with advanced malignancies treated with combined dendritic cell-activated T cell-based immunotherapy and intensity-modulated radiotherapy. Cancers. 3(2), 2223-2242.
DOI: https://doi.org/10.3390/cancers3022223

[30] Wang, X., Wang, Y., Chen, Z.G., et al., 2009. Advances of cancer therapy by nanotechnology. Cancer Research and Treatment. 41(1).
DOI: https://doi.org/10.4143/crt.2009.41.1.1

[31] Chaudhry, G.E., Islamiah, M., Ismail, N., et al., 2018. Induction of apoptosis by Aaptos sp., fractions in human breast cancer cell line, MCF-7. International Journal of Research in Pharmaceutical Science. 9(2), 328-337.

[32] Garcia-Oliveira, P., Otero, P., Pereira, A.G., et al., 2021. Status and challenges of plant-anticancer compounds in cancer treatment. Pharmaceuticals. 14(2), 157.
DOI: https://doi.org/10.3390/ph14020157

[33] Chaudhry, G.E., Akim, A.M., Sung, Y.Y., et al., 2022. Cancer and apoptosis. Methods in molecular biology. 2543, 191-210.
DOI: https://doi.org/10.1007/978-1-0716-2553-8_16

[34] Song, Y.H., Sun, H., Zhang, A.H., et al., 2014. Plant-derived natural products as leads to anti-cancer drugs. Journal of Medicinal Plant and Herbal Therapy Research. 2, 6-15.

[35] Nabeelah Bibi, S., Fawzi, M.M., Gokhan, Z., et al., 2019. Ethnopharmacology, phytochemistry, and global distribution of Mangroves—A comprehensive review. Marine Drugs. 17(4), 231.
DOI: https://doi.org/10.3390/md17040231

[36] Chaudhry, G.E., Rahman, N.H., Sevakumaran, V., et al., 2020. Induction of cytotoxicity by Bruguiera gymnorrhiza in human breast carcinoma (MCF-7) cell line via activation of the intrinsic pathway. Journal of Advanced Pharmaceutical Technology & Research. 11(4), 233-237.

[37] Chaudhry, G.E., Jan, R., Mohamad, H., et al., 2019. Vitex rotundifolia fractions induce apoptosis in human breast cancer cell line, MCF-7, via extrinsic

and intrinsic pathways. Research in Pharmaceutical Sciences. 14(3), 273-285.
DOI: https://doi.org/10.4103/1735-5362.258496

[38] Sithranga Boopathy, N., Kathiresan, K., 2010. Anticancer drugs from marine flora: An overview. Journal of Oncology. 214186.
DOI: https://doi.org/10.1155/2010/214186

[39] Jan, R., Zafar, M.N., Sung, Y.Y., et al., 2020. Phytochemistry and biological activity of Vitex rotundifolia L. Research Journal of Pharmacy and Technology. 13(11), 5534-5538.

[40] Barnes, J., Heinrich, M., 2004. Fundamentals of pharmacognosy and phytotherapy. Churchill Livingstone: London.

[41] Tag, H., Kalita, P., Dwivedi, P., et al., 2012. Herbal medicines used in the treatment of diabetes mellitus in Arunachal Himalaya, northeast, India. Journal of Ethnopharmacology. 141(3), 786-795.
DOI: https://doi.org/10.1016/j.jep.2012.03.007

[42] Twilley, D., Lall, N., 2018. The role of natural products from plants in the development of anticancer agents. Natural products and drug discovery. Elsevier: Amsterdam. pp 139-178.
DOI: https://doi.org/10.1016/B978-0-08-102081-4.00007-1

[43] Choudhari, A.S., Mandave, P.C., Deshpande, M., et al., 2020. Phytochemicals in cancer treatment: From preclinical studies to clinical practice. Frontiers in Pharmacology. 10, 1614.
DOI: https://doi.org/10.3389/fphar.2019.01614

[44] Gaston, T.E., Mendrick, D.L., Paine, M.F., et al., 2020. "Natural" is not synonymous with "Safe": Toxicity of natural products alone and in combination with pharmaceutical agents. Regulatory Toxicology and Pharmacology. 113, 104642.
DOI: https://doi.org/10.1016/j.yrtph.2020.104642

[45] Haq, I., 2004. Safety of medicinal plants. Pakistan Journal of Medical Research. 43(4), 203-210.

[46] Bent, S., 2008. Herbal medicine in the United States: Review of efficacy, safety, and regulation. Journal of General Internal Medicine. 23, 854-859.
DOI: https://doi.org/10.1007/s11606-008-0632-y

[47] Capasso, F., Gaginella, T.S., Grandolini, G., et al., 2003. The complexity of herbal medicines. Phytotherapy. Springer: Berlin, Heidelberg. pp. 11-12.
DOI: https://doi.org/10.1007/978-3-642-55528-2_4

[48] Ghosh, N., Ghosh, R.C., Kundu, A., et al., 2018. Herb and drug interaction. Natural products and drug discovery. Elsevier: Amsterdam. pp. 467-490.
DOI: https://doi.org/10.1016/B978-0-08-102081-4.00017-4

[49] Raoufinejad, K., Gholami, K., Javadi, M., et al., 2020. A retrospective cohort study of herbal medicines use during pregnancy: Prevalence, adverse reactions, and newborn outcomes. Traditional Integrative Medicine.
DOI: https://doi.org/10.18502/tim.v5i2.3627

[50] Heydari, M., Rauf, A., Thiruvengadam, M., et al., 2022. Editorial: Clinical safety of natural products, an evidence-based approach. Frontiers in Pharmacology. 13, 960556.
DOI: https://doi.org/10.3389/fphar.2022.960556

[51] Gadelha, I.C., Fonseca, N.B., Oloris, S.C., et al., 2014. Gossypol toxicity from cottonseed products. The Scientific World Journal. 231635.
DOI: https://doi.org/10.1155/2014/231635

[52] Kenar, J.A., 2006. Reaction chemistry of gossypol and its derivatives. Journal of the American Oil Chemists' Society. 83(4), 269-302.
DOI: https://doi.org/10.1007/s11746-006-1203-1

[53] Renner, O., Mayer, M., Leischner, C., et al., 2022. Systematic review of Gossypol/AT-101 in cancer clinical trials. Pharmaceuticals. 15(2), 144.
DOI: https://doi.org/10.3390/ph15020144

[54] Abou-Donia, M.B., 1976. Physiological effects and metabolism of gossypol. Residue Reviews. 61, 125-160.
DOI: https://doi.org/10.1007/978-1-4613-9401-3_5

[55] Rogers, G.M., Poore, M.H., Paschal, J.C., 2002. Feeding cotton products to cattle. Veterinary Clinics: Food Animal Practice. 18(2), 267-294.
DOI: https://doi.org/10.1016/s0749-0720(02)00020-8

[56] PubChem Compound Summary for CID 3503, Gossypol [Internet]. National Center for Biotechnology Information; 2023. [cited 2023 Sep 19]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Gossypol

[57] Zeng, Y., Ma, J., Xu, L., et al., 2019. Natural product gossypol and its derivatives in precision cancer medicine. Current Medicinal Chemistry. 26(10), 1849-1873.
DOI: https://doi.org/10.2174/0929867324666170523123655

[58] Volate, S.R., Kawasaki, B.T., Hurt, E.M., et al., 2010. Gossypol induces apoptosis by activating p53 in prostate cancer cells and prostate tumor—initiating cells. Molecular Cancer Therapeutics. 9(2), 461-470.
DOI: https://doi.org/10.1158/1535-7163.MCT-09-0507

[59] Moon, D.O., Choi, Y.H., Moon, S.K., et al., 2011. Gossypol decreases tumor necrosis factor-α-induced intercellular adhesion molecule-1 expression via suppression of NF-κB activity. Food and Chemical Toxicology. 49(4), 999-1005.
DOI: https://doi.org/10.1016/j.fct.2011.01.006

[60] Xiong, J., Li, J., Yang, Q., et al., 2017. Gossypol has anti-cancer effects by dual-targeting MDM2 and VEGF in human breast cancer. Breast Cancer Research. 19(1), 27.
DOI: https://doi.org/10.1186/s13058-017-0818-5

[61] Huang, Y.W., Wang, L.S., Dowd, M.K., et al., 2009. (-)-Gossypol reduces invasiveness in metastatic prostate cancer cells. Anticancer Research. 29(6), 2179-2188.

[62] Lee, S., Hong, E., Jo, E., et al., 2022. Gossypol induces apoptosis of human pancreatic cancer cells via CHOP/endoplasmic reticulum stress signaling pathway. Journal of Microbiology and Biotechnology. 32(5), 645-656.
DOI: https://doi.org/10.4014/jmb.2110.10019

[63] Jiang, J., Sugimoto, Y., Liu, S., et al., 2004. The inhibitory effects of gossypol on human prostate cancer cells-PC3 are associated with transforming growth factor beta1 (TGFβ1) signal transduction pathway. Anticancer Research. 24(1), 91-100.

[64] Clément, M.O., 2017. Gossypol: A potential promising anticancer agent. Scholar Academic Journal of Pharmacy. 6(6), 236-244.
DOI: https://doi.org/10.21276/sajp

[65] Qian, S., Wang, Z., 1984. Gossypol: A potential antifertility agent for males. Annual Review of Pharmacology and Toxicology. 24(1), 329-360.
DOI: https://doi.org/10.1146/annurev.pa.24.040184.001553

[66] Van Poznak, C., Seidman, A.D., Reidenberg, M.M., et al., 2001. Oral gossypol in the treatment of patients with refractory metastatic breast cancer: A phase I/II clinical trial. Breast Cancer Research and Treatment. 66, 239-248.
DOI: https://doi.org/10.1023/A:1010686204736

[67] Stein, M.N., Goodin, S., Gounder, M., et al., 2020. A phase I study of AT-101, a BH3 mimetic, in combination with paclitaxel and carboplatin in solid tumors. Investigational New Drugs. 38, 855-865.
DOI: https://doi.org/10.1007/s10637-019-00807-2

[68] Xie, H., Yin, J., Shah, M.H., et al., 2019. A phase II study of the orally administered negative enantiomer of gossypol (AT-101), a BH3 mimetic, in patients with advanced adrenal cortical carcinoma. Investigational New Drugs. 37, 755-762.
DOI: https://doi.org/10.1007/s10637-019-00797-1

[69] Baggstrom, M.Q., Qi, Y., Koczywas, M., et al., 2011. A phase II study of AT-101 (Gossypol) in chemotherapy-sensitive recurrent extensive-stage small cell lung cancer. Journal of Thoracic Oncology. 6(10), 1757-1760.
DOI: https://doi.org/10.1097/JTO.0b013e31822e2941

[70] Bushunow, P., Reidenberg, M.M., Wasenko, J., et al., 1999. Gossypol treatment of recurrent adult malignant gliomas. Journal of Neuro-oncology. 43, 79-86.
DOI: https://doi.org/10.1023/A:1006267902186

[71] Wang, Y., Li, X., Zhang, L., et al., 2020. A randomized, double-blind, placebo-controlled study of B-cell lymphoma 2 homology 3 mimetic gossypol combined with docetaxel and cisplatin for advanced non-small cell lung cancer with high expression of apurinic/apyrimidinic endonuclease 1. Investigational New Drugs. 38, 1862-1871.
DOI: https://doi.org/10.1007/s10637-020-00927-0

[72] Swiecicki, P.L., Bellile, E., Sacco, A.G., et al., 2016. A phase II trial of the BCL-2 homolog domain 3 mimetic AT-101 in combination with docetaxel for recurrent, locally advanced, or metastatic head and neck cancer. Investigational New Drugs. 34, 481-489.
DOI: https://doi.org/10.1007/s10637-016-0364-5

[73] Stein, M.N., Hussain, M., Stadler, W.M., et al., 2016. A Phase II study of AT-101 to overcome Bcl-2 mediated resistance to androgen deprivation therapy in patients with newly diagnosed castration-sensitive metastatic prostate cancer. Clinical Genitourinary Cancer. 14(1), 22-27.
DOI: https://doi.org/10.1016/j.clgc.2015.09.010

[74] Schelman, W.R., Mohammed, T.A., Traynor, A.M., et al., 2014. A phase I study of AT-101 with cisplatin and etoposide in patients with advanced solid tumors with an expanded cohort in extensive-stage small cell lung cancer. Investigational New Drugs. 32, 295-302.
DOI: https://doi.org/10.1007/s10637-013-9999-7

[75] Sonpavde, G., Matveev, V., Burke, J.M., et al., 2012. Randomized phase II trial of docetaxel plus prednisone in combination with placebo or AT-101, an oral small molecule Bcl-2 family antagonist, as first-line therapy for metastatic castration-resistant prostate cancer. Annals of Oncology. 23(7), 1803-1808.
DOI: https://doi.org/10.1093/annonc/mdr555

[76] Ready, N., Karaseva, N.A., Orlov, S.V., et al., 2011. Double-blind, placebo-controlled, randomized

phase 2 study of the proapoptotic agent AT-101 plus docetaxel, in second-line non-small cell lung cancer. Journal of Thoracic Oncology. 6(4), 781-785.
DOI: https://doi.org/10.1097/JTO.0b013e31820a0ea6

[77] Heist, R.S., Fain, J., Chinnasami, B., et al., 2010. Phase I/II study of AT-101 with topotecan in relapsed and refractory small cell lung cancer. Journal of Thoracic Oncology. 5(10), 1637-1643.
DOI: https://doi.org/10.1097/JTO.0b013e3181e8f-4dc

[78] de Peyster, A., Wang, Y.Y., 1993. Genetic toxicity studies of gossypol. Mutation Research. 297(3), 293-312.
DOI: https://doi.org/10.1016/0165-1110(93)90021-e

[79] Waites, G.M., Wang, C., Griffin, P.D., 1998. Gossypol: Reasons for its failure to be accepted as a safe, reversible male antifertility drug. International Journal of Andrology. 21(1), 8-12.
DOI: https://doi.org/10.1046/j.1365-2605.1998.00092.x

[80] Quintana, P.J., de Peyster, A., Klatzke, S., et al., 2000. Gossypol-induced DNA breaks in rat lymphocytes are secondary to cytotoxicity. Toxicology Letters. 117(1-2), 85-94.
DOI: https://doi.org/10.1016/s0378-4274(00)00244-7

[81] Pal, D., Sahu, P., Sethi, G., et al., 2022. Gossypol and its natural derivatives: Multitargeted phytochemicals as potential drug candidates for oncologic diseases. Pharmaceutics. 14(12), 2624.
DOI: https://doi.org/10.3390/pharmaceutics14122624

[82] Giordano, A., Tommonaro, G., 2019. Curcumin and cancer. Nutrients. 11(10), 2376.
DOI: https://doi.org/10.3390/nu11102376

[83] PubChem Compound Summary for CID 969516, Curcumin [Internet]. National Center for Biotechnology Information; 2023. [cited 2023 Sep 19]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Curcumin

[84] Pulido-Moran, M., Moreno-Fernandez, J., Ramirez-Tortosa, C., et al., 2016. Curcumin and health. Molecules. 21(3), 264.
DOI: https://doi.org/10.3390/molecules21030264

[85] Barchitta, M., Maugeri, A., Favara, G., et al., 2019. Nutrition and wound healing: An overview focusing on the beneficial effects of curcumin. International Journal of Molecular Sciences. 20(5), 1119.
DOI: https://doi.org/10.3390/ijms20051119

[86] Mantzorou, M., Pavlidou, E., Vasios, G., et al., 2018. Effects of curcumin consumption on human chronic diseases: A narrative review of the most recent clinical data. Phytotherapy Research. 32(6), 957-975.
DOI: https://doi.org/10.1002/ptr.6037

[87] Tan, R.Z., Liu, J., Zhang, Y.Y., et al., 2019. Curcumin relieved cisplatin-induced kidney inflammation through inhibiting Mincle-maintained M1 macrophage phenotype. Phytomedicine. 52, 284-294.
DOI: https://doi.org/10.1016/j.phymed.2018.09.210

[88] Tan, B.L., Norhaizan, M.E., 2019. Curcumin combination chemotherapy: The implication and efficacy in cancer. Molecules. 24(14), 2527.
DOI: https://doi.org/10.3390/molecules24142527

[89] Kunnumakkara, A.B., Bordoloi, D., Padmavathi, G., et al., 2017. Curcumin, the golden nutraceutical: Multitargeting for multiple chronic diseases. British Journal of Pharmacology. 174(11), 1325-1348.
DOI: https://doi.org/10.1111/bph.13621

[90] Anand, P., Sundaram, C., Jhurani, S., et al., 2008. Curcumin and cancer: An "old-age" disease with an "age-old" solution. Cancer Letters. 267(1), 133-164.
DOI: https://doi.org/10.1016/j.canlet.2008.03.025

[91] Tomeh, M.A., Hadianamrei, R., Zhao, X., 2019. A review of curcumin and its derivatives as anticancer agents. International Journal of Molecular Sciences. 20(5), 1033.
DOI: https://doi.org/10.3390/ijms20051033

[92] Watson, J.L., Greenshields, A., Hill, R., et al., 2010. Curcumin-induced apoptosis in ovarian carcinoma cells is p53-independent and involves p38 mitogen-activated protein kinase activation and downregulation of Bcl-2 and survivin expression and Akt signaling. Molecular Carcinogenesis. 49(1), 13-24.
DOI: https://doi.org/10.1002/mc.20571

[93] Pourhanifeh, M.H., Darvish, M., Tabatabaeian, J., et al., 2020. Therapeutic role of curcumin and its novel formulations in gynecological cancers. Journal of Ovarian Research. 13, 130.
DOI: https://doi.org/10.1186/s13048-020-00731-7

[94] Hewlings, S.J., Kalman, D.S., 2017. Curcumin: A review of its effects on human health. Foods. 6(10), 92.
DOI: https://doi.org/10.3390/foods6100092

[95] Nelson, K.M., Dahlin, J.L., Bisson, J., et al., 2017. The essential medicinal chemistry of curcumin. Journal of Medicinal Chemistry. 60(5), 1620-1637.
DOI: https://doi.org/10.1021/acs.jmedchem.6b00975

[96] Walker, B.C., Mittal, S., 2020. Antitumor activity of curcumin in glioblastoma. International Journal of Molecular Sciences. 21(24), 9435.

DOI: https://doi.org/10.3390/ijms21249435

[97] Chan, E.W.C., Wong, C.W., Tan, Y.H., et al., 2019. Resveratrol and pterostilbene: A comparative overview of their chemistry, biosynthesis, plant sources and pharmacological properties. Journal of Applied Pharmaceutical Science. 9(7), 124-129. DOI: https://doi.org/10.7324/JAPS.2019.90717

[98] Intagliata, S., Modica, M.N., Santagati, L.M., et al., 2019. Strategies to improve resveratrol systemic and topical bioavailability: An update. Antioxidants. 8(8), 244. DOI: https://doi.org/10.3390/antiox8080244

[99] Ahmadi, R., Ebrahimzadeh, M.A., 2020. Resveratrol—A comprehensive review of recent advances in anticancer drug design and development. European Journal of Medicinal Chemistry. 200, 112356. DOI: https://doi.org/10.1016/j.ejmech.2020.112356

[100] PubChem Compound Summary for CID 445154, Resveratrol [Internet]. National Center for Biotechnology Information; 2023. [cited 2023 Sep 19]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Resveratrol

[101] Jang, M., Cai, L., Udeani, G.O., et al., 1997. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science. 275(5297), 218-220. DOI: https://doi.org/10.1126/science.275.5297.218

[102] Baur, J.A., Sinclair, D.A., 2006. Therapeutic potential of resveratrol: The in vivo evidence. Nature Reviews Drug Discovery. 5, 493-506. DOI: https://doi.org/10.1038/nrd2060

[103] Athar, M., Back, J.H., Tang, X., et al., 2007. Resveratrol: A review of preclinical studies for human cancer prevention. Toxicology and Applied Pharmacology. 224(3), 274-283. DOI: https://doi.org/10.1016/j.taap.2006.12.025

[104] Shukla, Y., Singh, R., 2011. Resveratrol and cellular mechanisms of cancer prevention. Annals of the New York Academy of Sciences. 1215(1), 1-8. DOI: https://doi.org/10.1111/j.1749-6632.2010.05870.x

[105] Nakagawa, H., Kiyozuka, Y., Uemura, Y., et al., 2001. Resveratrol inhibits human breast cancer cell growth and may mitigate the effect of linoleic acid, a potent breast cancer cell stimulator. Journal of Cancer Research and Clinical Oncology. 127, 258-264. DOI: https://doi.org/10.1007/s004320000190

[106] Joe, A.K., Liu, H., Suzui, M., et al., 2002. Resveratrol induces growth inhibition, S-phase arrest, apoptosis, and changes in biomarker expression in several human cancer cell lines. Clinical Cancer Research. 8(3), 893-903.

[107] Shih, A., Davis, F.B., Lin, H.Y., et al., 2002. Resveratrol induces apoptosis in thyroid cancer cell lines via a MAPK-and p53-dependent mechanism. The Journal of Clinical Endocrinology & Metabolism. 87(3), 1223-1232. DOI: https://doi.org/10.1210/jcem.87.3.8345

[108] Roman, V., Billard, C., Kern, C., et al., 2002. Analysis of resveratrol-induced apoptosis in human B-cell chronic leukaemia. British Journal of Haematology. 117(4), 842-851. DOI: https://doi.org/10.1046/j.1365-2141.2002.03520.x

[109] Liang, Y.C., Tsai, S.H., Chen, L., et al., 2003. Resveratrol-induced G2 arrest through the inhibition of CDK7 and p34CDC2 kinases in colon carcinoma HT29 cells. Biochemical Pharmacology. 65(7), 1053-1060. DOI: https://doi.org/10.1016/s0006-2952(03)00011-x

[110] Liao, P.C., Ng, L.T., Lin, L.T., et al., 2010. Resveratrol arrests cell cycle and induces apoptosis in human hepatocellular carcinoma Huh-7 cells. Journal of Medicinal Food. 13(6), 1415-1423. DOI: https://doi.org/10.1089/jmf.2010.1126

[111] Park, J.W., Choi, Y.J., Suh, S.I., et al., 2001. Bcl-2 overexpression attenuates resveratrol-induced apoptosis in U937 cells by inhibition of caspase-3 activity. Carcinogenesis. 22(10), 1633-1639. DOI: https://doi.org/10.1093/carcin/22.10.1633

[112] Wolter, F., Akoglu, B., Clausnitzer, A., et al., 2001. Downregulation of the cyclin D1/Cdk4 complex occurs during resveratrol-induced cell cycle arrest in colon cancer cell lines. The Journal of Nutrition. 131(8), 2197-2203. DOI: https://doi.org/10.1093/jn/131.8.2197

[113] Gao, X., Xu, Y.X., Divine, G., et al., 2002. Disparate in vitro and in vivo antileukemic effects of resveratrol, a natural polyphenolic compound found in grapes. The Journal of Nutrition. 132(7), 2076-2081. DOI: https://doi.org/10.1093/jn/132.7.2076

[114] Mouria, M., Gukovskaya, A.S., Jung, Y., et al., 2002. Food-derived polyphenols inhibit pancreatic cancer growth through mitochondrial cytochrome C release and apoptosis. International Journal of Cancer. 98(5), 761-769. DOI: https://doi.org/10.1002/ijc.10202

[115] Mahyar-Roemer, M., Katsen, A., Mestres, P., et al., 2001. Resveratrol induces colon tumor cell apoptosis independently of p53 and precede by epithelial differentiation, mitochondrial proliferation and membrane potential collapse. International Journal of Cancer. 94(5), 615-622. DOI: https://doi.org/10.1002/ijc.1516

[116] Huang, C., Ma, W.Y., Goranson, A., et al., 1999. Resveratrol suppresses cell transformation and induces apoptosis through a p53-dependent pathway. Carcinogenesis. 20(2), 237-242.
DOI: https://doi.org/10.1093/carcin/20.2.237

[117] Kuo, P.L., Chiang, L.C., Lin, C.C., 2002. Resveratrol-induced apoptosis is mediated by p53-dependent pathway in Hep G2 cells. Life Sciences. 72(1), 23-34.
DOI: https://doi.org/10.1016/s0024-3205(02)02177-x

[118] Takashina, M., Inoue, S., Tomihara, K., et al., 2017. Different effect of resveratrol to induction of apoptosis depending on the type of human cancer cells. International Journal of Oncology. 50(3), 787-797.
DOI: https://doi.org/10.3892/ijo.2017.3859

[119] Cottart, C.H., Nivet-Antoine, V., Laguillier-Morizot, C., et al., 2010. Resveratrol bioavailability and toxicity in humans. Molecular nutrition & Food Research. 54(1), 7-16.
DOI: https://doi.org/10.1002/mnfr.200900437

[120] Crowell, J.A., Korytko, P.J., Morrissey, R.L., et al., 2004. Resveratrol-associated renal toxicity. Toxicological Sciences. 82(2), 614-619.
DOI: https://doi.org/10.1093/toxsci/kfh263

[121] Juan, M.E., Vinardell, M.P., Planas, J.M., 2002. The daily oral administration of high doses of trans-resveratrol to rats for 28 days is not harmful. The Journal of Nutrition. 132(2), 257-260.
DOI: https://doi.org/10.1093/jn/132.2.257

[122] Williams, L.D., Burdock, G.A., Edwards, J.A., et al., 2009. Safety studies conducted on high-purity trans-resveratrol in experimental animals. Food and Chemical Toxicology. 47(9), 2170-2182.
DOI: https://doi.org/10.1016/j.fct.2009.06.002

[123] Boocock, D.J., Faust, G.E., Patel, K.R., et al., 2007. Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent. Cancer Epidemiology Biomarkers & Prevention. 16(6), 1246-1252.
DOI: https://doi.org/10.1158/1055-9965.EPI-07-0022

[124] Vaz-da-Silva, M., Loureiro, A.I., Falcao, A., et al., 2008. Effect of food on the pharmacokinetic profile of trans-resveratrol. International Journal of Clinical Pharmacology and Therapeutics. 46(11), 564-570.
DOI: https://doi.org/10.5414/cpp46564

[125] Almeida, L., Vaz-da-Silva, M., Falcão, A., et al., 2009. Pharmacokinetic and safety profile of trans-resveratrol in a rising multiple-dose study in healthy volunteers. Molecular Nutrition & Food Research. 53(S1), S7-S15.
DOI: https://doi.org/10.1002/mnfr.200800177

[126] Ashrafizadeh, M., Najafi, M., Orouei, S., et al., 2020. Resveratrol modulates transforming growth factor-beta (tgf-β) signaling pathway for disease therapy: A new insight into its pharmacological activities. Biomedicines. 8(8), 261.
DOI: https://doi.org/10.3390/biomedicines8080261

[127] Patel, K.R., Scott, E., Brown, V.A., et al., 2011. Clinical trials of resveratrol. Annals of the New York Academy of Sciences. 1215(1), 161-169.
DOI: https://doi.org/10.1111/j.1749-6632.2010.05853.x

[128] Salehi, B., Mishra, A.P., Nigam, M., et al., 2018. Resveratrol: A double-edged sword in health benefits. Biomedicines. 6(3), 91.
DOI: https://doi.org/10.3390/biomedicines6030091

[129] PubChem Compound Summary for CID 5281628, Hispidulin [Internet]. National Center for Biotechnology Information; 2023. [cited 2023 Sep 19]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Hispidulin

[130] Cui, B., Lee, Y.H., Chai, H., et al., 1999. Cytotoxic sesquiterpenoids from Ratibida columnifera. Journal of Natural Products. 62(11), 1545-1550.
DOI: https://doi.org/10.1021/np990260y

[131] Flamini, G., Antognoli, E., Morelli, I., 2001. Two flavonoids and other compounds from the aerial parts of Centaurea bracteata from Italy. Phytochemistry. 57(4), 559-564.
DOI: https://doi.org/10.1016/s0031-9422(01)00066-8

[132] Fullas, F., Hussain, R.A., Chai, H.B., et al., 1994. Cytotoxic constituents of Baccharis gaudichaudiana. Journal of Natural Products. 57(6), 801-807.
DOI: https://doi.org/10.1021/np50108a017

[133] Kavvadias, D., Monschein, V., Sand, P., et al., 2003. Constituents of sage (Salvia officinalis) with in vitro affinity to human brain benzodiazepine receptor. Planta Medica. 69(2), 113-117.
DOI: https://doi.org/10.1055/s-2003-37712

[134] Chao, S.W., Su, M.Y., Chiou, L.C., et al., 2015. Total synthesis of hispidulin and the structural basis for its inhibition of proto-oncogene kinase Pim-1. Journal of Natural Products. 78(8), 1969-1976.
DOI: https://doi.org/10.1021/acs.jnatprod.5b00324

[135] Liu, K., Zhao, F., Yan, J., et al., 2020. Hispidulin: A promising flavonoid with diverse anti-cancer properties. Life Sciences. 259, 118395.
DOI: https://doi.org/10.1016/j.lfs.2020.118395

[136] Chaudhry, G.E., Zeenia, Sharifi-Rad, J., Calina, D., 2023. Hispidulin: A promising anticancer agent and mechanistic breakthrough for targeted cancer therapy. Naunyn-Schmiedeberg's Archives of Pharmacol-

ogy.
DOI: https://doi.org/10.1007/s00210-023-02645-9

[137] Lv, L., Zhang, W., Li, T., et al., 2020. Hispidulin exhibits potent anticancer activity in vitro and in vivo through activating ER stress in non-small-cell lung cancer cells. Oncology Reports. 43(6), 1995-2003.
DOI: https://doi.org/10.3892/or.2020.7568

[138] Yadav, A.K., Thakur, J., Prakash, O.M., et al., 2013. Screening of flavonoids for antitubercular activity and their structure—activity relationships. Medicinal Chemistry Research. 22, 2706-2716.
DOI: https://doi.org/10.1007/s00044-012-0268-7

[139] Atif, M., Ali, I., Hussain, A., et al., 2015. Pharmacological assessment of hispidulin—a natural bioactive flavone. Acta Poloniae Pharmaceutica. 72(5), 829-842.

[140] Zhai, K., Mazurakova, A., Koklesova, L., et al., 2021. Flavonoids synergistically enhance the anti-glioblastoma effects of chemotherapeutic drugs. Biomolecules. 11(12), 1841.
DOI: https://doi.org/10.3390/biom11121841

[141] Tuli, H.S., Tuorkey, M.J., Thakral, F., et al., 2019. Molecular mechanisms of action of genistein in cancer: Recent advances. Frontiers in Pharmacology. 10, 1336.
DOI: https://doi.org/10.3389/fphar.2019.01336

[142] Goh, Y.X., Jalil, J., Lam, K.W., et al., 2022. Genistein: A review on its anti-inflammatory properties. Frontiers in Pharmacology. 13, 820969.
DOI: https://doi.org/10.3389/fphar.2022.820969

[143] PubChem Compound Summary for CID 5280961, Genistein [Internet]. National Center for Biotechnology Information; 2023. [cited 2023 Sep 19]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Genistein

[144] Sharifi-Rad, J., Quispe, C., Imran, M., et al., 2021. Genistein: An integrative overview of its mode of action, pharmacological properties, and health benefits. Oxidative Medicine and Cellular Longevity. 3268136.
DOI: https://doi.org/10.1155/2021/3268136

[145] Peterson, G., Barnes, S., 1996. Genistein inhibits both estrogen and growth factor-stimulated proliferation of human breast cancer cells. Cell Growth and Differentiation-Publication American Association for Cancer Research. 7(10), 1345-1352.

[146] Matsukawa, Y., Marui, N., Sakai, T., et al., 1993. Genistein arrests cell cycle progression at G2-M. Cancer Research. 53(6), 1328-1331.

[147] Farina, H.G., Pomies, M., Alonso, D.F., et al., 2006. Antitumor and antiangiogenic activity of soy isoflavone genistein in mouse models of melanoma and breast cancer. Oncology Reports. 16(4), 885-891.
DOI: https://doi.org/10.3892/or.16.4.885

[148] Sarkar, F.H., Adsule, S., Padhye, S., et al., 2006. The role of genistein and synthetic derivatives of isoflavone in cancer prevention and therapy. Mini Reviews in Medicinal Chemistry. 6(4), 401-407.
DOI: https://doi.org/10.2174/138955706776361439

[149] Huang, W., Wan, C., Luo, Q., et al., 2014. Genistein-inhibited cancer stem cell-like properties and reduced chemoresistance of gastric cancer. International Journal of Molecular Sciences. 15(3), 3432-3443.
DOI: https://doi.org/10.3390/ijms15033432

[150] Bloedon, L.T., Jeffcoat, A.R., Lopaczynski, W., et al., 2002. Safety and pharmacokinetics of purified soy isoflavones: Single-dose administration to postmenopausal women. The American Journal of Clinical Nutrition. 76(5), 1126-1137.
DOI: https://doi.org/10.1093/ajcn/76.5.1126

[151] Huang, Z.R., Hung, C.F., Lin, Y.K., et al., 2008. In vitro and in vivo evaluation of topical delivery and potential dermal use of soy isoflavones genistein and daidzein. International Journal of Pharmaceutics. 364(1), 36-44.
DOI: https://doi.org/10.1016/j.ijpharm.2008.08.002

[152] Bocheńska, K., Moskot, M., Smolińska-Fijołek, E., et al., 2021. Impact of isoflavone genistein on psoriasis in in vivo and in vitro investigations. Scientific Reports. 11(1), 18297.
DOI: https://doi.org/10.1038/s41598-021-97793-4

[153] Serebrenik, A.A., Verduyn, C.W., Kaytor, M.D., 2023. Safety, pharmacokinetics, and biomarkers of an amorphous solid dispersion of genistein, a radioprotectant, in healthy volunteers. Clinical Pharmacology in Drug Development. 12(2), 190-201.
DOI: https://doi.org/10.1002/cpdd.1188

[154] Cooper-Driver, G.A., 2001. Contributions of Jeffrey Harborne and co-workers to the study of anthocyanins. Phytochemistry. 56(3), 229-236.
DOI: https://doi.org/10.1016/s0031-9422(00)00455-6

[155] Sarma, A.D., Sreelakshmi, Y., Sharma, R., 1997. Antioxidant ability of anthocyanins against ascorbic acid oxidation. Phytochemistry. 45(4), 671-674.
DOI: https://doi.org/10.1016/S0031-9422(97)00057-5

[156] Lin, B.W., Gong, C.C., Song, H.F., et al., 2017. Effects of anthocyanins on the prevention and treatment of cancer. British Journal of Pharmacology. 174(11), 1226-1243.
DOI: https://doi.org/10.1111/bph.13627

[157] PubChem Compound Summary for CID 101115386

[Internet]. National Center for Biotechnology Information; 2023. [cited 2023 Sep 19]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/101115386

[158] Panchal, S.K., John, O.D., Mathai, M.L., et al., 2022. Anthocyanins in chronic diseases: The power of purple. Nutrients. 14(10), 2161.
DOI: https://doi.org/10.3390/nu14102161

[159] Burton-Freeman, B., Brzeziński, M., Park, E., et al., 2019. A selective role of dietary anthocyanins and flavan-3-ols in reducing the risk of type 2 diabetes mellitus: A review of recent evidence. Nutrients. 11(4), 841.
DOI: https://doi.org/10.3390/nu11040841

[160] Grosso, G., 2018. Effects of polyphenol-rich foods on human health. Nutrients. 10(8), 1089.
DOI: https://doi.org/10.3390/nu10081089

[161] Ho, M.L., Chen, P.N., Chu, S.C., et al., 2010. Peonidin 3-glucoside inhibits lung cancer metastasis by downregulation of proteinases activities and MAPK pathway. Nutrition and Cancer. 62(4), 505-516.
DOI: https://doi.org/10.1080/01635580903441261

[162] Afaq, F., Malik, A., Syed, D., et al., 2005. Pomegranate fruit extract modulates UV-B-mediated phosphorylation of mitogen-activated protein kinases and activation of nuclear factor kappa B in normal human epidermal keratinocytes. Photochemistry and Photobiology. 81(1), 38-45.
DOI: https://doi.org/10.1562/2004-08-06-RA-264

[163] Shin, D.Y., Lee, W.S., Lu, J.N., et al., 2009. Induction of apoptosis in human colon cancer HCT-116 cells by anthocyanins through suppression of Akt and activation of p38-MAPK. International Journal of Oncology. 35(6), 1499-1504.
DOI: https://doi.org/10.3892/ijo_00000469

[164] Giampieri, F., Cianciosi, D., Alvarez-Suarez, J.M., et al., 2023. Anthocyanins: What do we know until now?. Journal of Berry Research. 1-6.
DOI: https://doi.org/10.3233/JBR-220087

[165] Benot-Dominguez, R., Cimini, A., Barone, D., et al., 2022. The emerging role of cyclin-dependent kinase inhibitors in treating diet-induced obesity: New opportunities for breast and ovarian cancers?. Cancers. 14(11), 2709.
DOI: https://doi.org/10.3390/cancers14112709

[166] Ashwin, P.P., Sutar, N.G., Vishnu, A.S., et al., 2023. Anticancer activity of anthocyanins: A comprehensive review. Journal of Survey in Fisheries Sciences. 10(1S), 5993-6007.

[167] Forester, S.C., Waterhouse, A.L., 2010. Gut metabolites of anthocyanins, gallic acid, 3-O-methylgallic acid, and 2, 4, 6-trihydroxybenzaldehyde, inhibit cell proliferation of Caco-2 cells. Journal of Agricultural and Food Chemistry. 58(9), 5320-5327.
DOI: https://doi.org/10.1021/jf9040172

[168] Sehitoglu, M.H., Farooqi, A.A., Qureshi, M.Z., et al., 2014. Anthocyanins: Targeting of signaling networks in cancer cells. Asian Pacific Journal of Cancer Prevention. 15(5), 2379-2381.
DOI: https://doi.org/10.7314/apjcp.2014.15.5.2379

[169] Malik, M., Zhao, C., Schoene, N., et al., 2003. Anthocyanin-rich extract from aronia meloncarpa E. Induces a cell cycle block in colon cancer but not normal colonic cells. Nutrition & Cancer. 46(2), 186-196.
DOI: https://doi.org/10.1207/S15327914NC4602_12

[170] Wang, L.S., Stoner, G.D., 2008. Anthocyanins and their role in cancer prevention. Cancer Letters. 269(2), 281-290.
DOI: https://doi.org/10.1016/j.canlet.2008.05.020

[171] Reddivari, L., Vanamala, J., Chintharlapalli, S., et al., 2007. Anthocyanin fraction from potato extracts is cytotoxic to prostate cancer cells through activation of caspase-dependent and caspase-independent pathways. Carcinogenesis. 28(10), 2227-2235.
DOI: https://doi.org/10.1093/carcin/bgm117

[172] Chang, Y.C., Huang, H.P., Hsu, J.D., et al., 2005. Hibiscus anthocyanins rich extract-induced apoptotic cell death in human promyelocytic leukemia cells. Toxicology and Applied Pharmacology. 205(3), 201-212.
DOI: https://doi.org/10.1016/j.taap.2004.10.014

[173] Hientz, K., Mohr, A., Bhakta-Guha, D., et al., 2017. The role of p53 in cancer drug resistance and targeted chemotherapy. Oncotarget. 8(5), 8921.
DOI: https://doi.org/10.18632/oncotarget.13475

[174] Diaconeasa, Z.M., Frond, A.D., Ştirbu, I., et al., 2018. Anthocyanins—smart molecules for cancer prevention. Phytochemicals—Source of Antioxidants and Role in Disease Prevention. IntechOpen: London.
DOI: https://doi.org/10.5772/intechopen.79613

[175] Gull, A., Sheikh, M.A., Kour, J., et al., 2022. Anthocyanins. Nutraceuticals and health care. Academic Press: Cambridge. pp. 317-329.
DOI: https://doi.org/10.1016/B978-0-323-89779-2.00018-1

[176] Wallace, T.C., Giusti, M.M., 2015. Anthocyanins. Advances in Nutrition. 6(5), 620-622.
DOI: https://doi.org/10.3945/an.115.009233

[177] Morazzoni, P., Bombardelli, E., 1996. Vaccinium myrtillus L. Fitoterapia. 67, 3-29.

[178] He, J., Giusti, M.M., 2010. Anthocyanins: Natural colorants with health-promoting properties. Annual Review of Food Science and Technology. 1, 163-187.
DOI: https://doi.org/10.1146/annurev.food.080708.100754

[179] Gonçalves, A.C., Nunes, A.R., Falcão, A., et al., 2021. Dietary effects of anthocyanins in human health: A comprehensive review. Pharmaceuticals. 14(7), 690.
DOI: https://doi.org/10.3390/ph14070690