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Honors Undergraduate Thesis- Nutritional Sciences Department

Dietary Histone Deacetylase Inhibitors in Chemoprevention

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Introduction

Cancer has remained the second leading cause of death in the United States, with the gap between that and the number one cause, heart disease, decreasing significantly over the past 50 years. As the prevalence of cancer increases throughout the United States, research continues to analyze new aspects of its prevention and treatment (Heron & Anderson, 2016). Within the field of nutrition, it has become increasingly apparent the importance of preventative medicine through dietary components. A recent area of interest within the field of nutrition and epigenetics is the use of histone deacetylase (HDAC) inhibitors as chemopreventative agents.

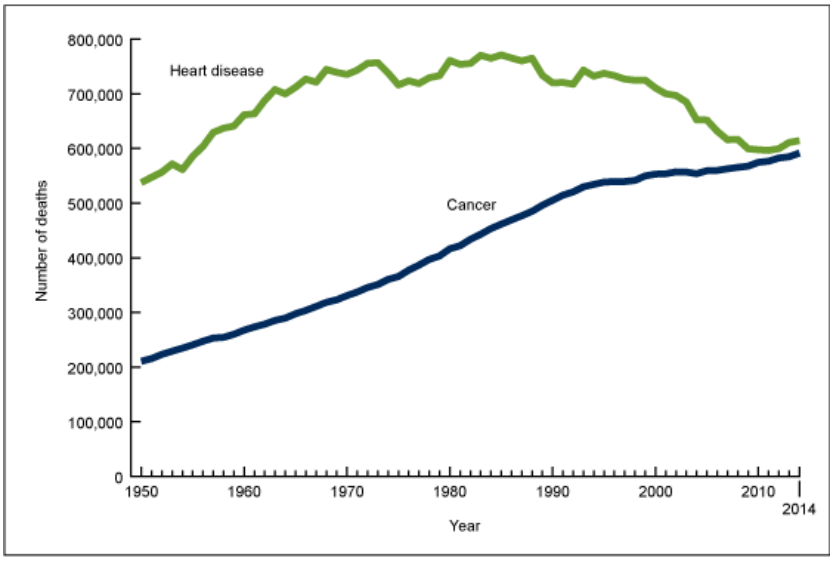

Figure 1. (Heron, Melonie & Anderson, Robert, 2016, Number of deaths due to heart disease and cancer: United States, 1950-2014, [Source: NCHS, National Vital Statistics System, Mortality]).

Chemotherapy and Chemoprevention

Chemotherapy is the use of medicinal drugs to treat cancer, and is often times used in combination with surgery and/or radiation (The American Cancer Society medical and editorial content team, 2016). When determining the most effective treatment regimen, doctors take into consideration the type and stage of cancer, as well as the patient's age and overall health.

Chemotherapy can be used prior to surgery or radiation to shrink the tumor, while surgery can then be used to remove it. Chemotherapy and surgery are frequently followed by radiation, which aims to kill any remaining cancer cells (The American Cancer Society medical and editorial content team, 2016). However, depending on the size and type of cancer, different combinations of these treatments may or may not be used. The importance of chemotherapy in treating cancer is its ability to not only kill localized cancer cells, but also cancer cells that have metastasized, or spread to another area in the body. Chemotherapy drugs work by targeting the cell cycle at different phases in order to terminate, or at least control, cancer cell progression. However, chemotherapeutic drugs cannot differentiate between normal, healthy cells and cancerous cells. The subsequent damage to normal cells during chemotherapy can lead to numerous side effects including changes in behavior, dehydration, eating problems associated with changing or damaged taste buds, fatigue, hair loss, nausea, seizures, weight loss, and weakness. The accompanying side effects that follow chemotherapy have had researchers searching for new treatments that lack such harmful outcomes. (The American Cancer Society medical and editorial content team, 2016). Chemoprevention, the focus of this paper, is defined in *Food as a Source of Anticancerigen Compound,* as "the use of dietary agents to prevent the development or progression of cancer," (Hernandez & Chien, 2015). The study of chemoprevention is where researchers have begun focusing on compounds and components of the diet and their effects.

Histone Acetylation and Deacetylation

Within the field of epigenetics and oncology, it has been discovered that histone acetylation and deacetylation is an important mechanism for chemoprevention (Ho, Clarke, & Ashwood, 2009). Acetylation and deacetylation of nuclear histones is carried out via histone acetyltransferases

(HATs) and histone deacetylases (HDACs), respectively. Histone acetyltransferases result in an "open" conformation of chromatin, known as euchromatin, while histone deacetylases catalyze in a "closed" conformation, known as heterochromatin. The importance of HATs and HDACs in cancer prevention and/or suppressed progression is the role that they play in strictly regulating the conformation of DNA and the availability of DNA to be acted upon by transcription factors. While in the "open" conformation, due to HATs, DNA is exposed to transcription factors, and therefore, can undergo transcription. While in the "closed" conformation, due to HDACs, the transcription factors do not have access to DNA, and transcription is suppressed. Deacetylation, via HDACs, also results in tumor suppressing genes being repressed, or "turned off" (Mariadason, 2008). The balance between acetylation and deacetylation via HATs and HDACs influences gene expression by allowing or preventing transcription factors, chromatin remodeling, and other activation/repression mechanisms. This strictly regulated balance between acetylation and deacetylation is important for gene regulation and progression of cell growth.

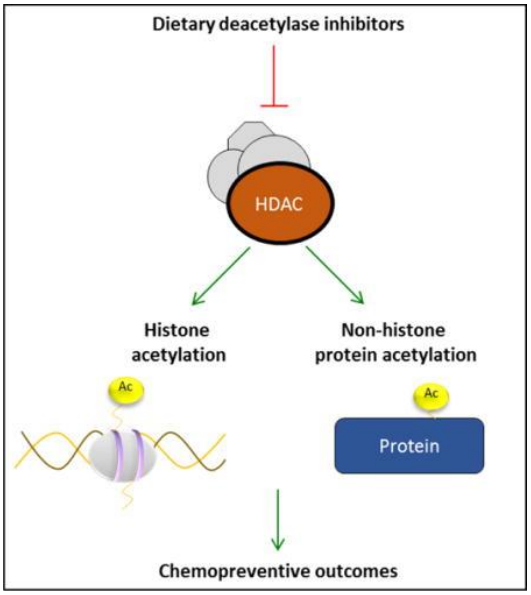

Figure 2. (Kim, Bisson, Lohr, Williams, Ho, Dashwood, Rajendran, 2016. Histone and Non-Histone Targets of Dietary Deacetylase Inhibitors).

Histone Deacetylases

Histone deacetylases are of particular interest in the development of cancer, as they function to close the chromatin conformation of DNA, preventing it from being acted upon by transcription factors (Ho, et.al, 2009). While HATs function to add an acetyl group to nuclear histones, HDACs work in opposition to remove an acetyl group. Histone deacetylates can also mechanistically alter non-histone proteins such as transcription factors, DNA repair mechanisms, and tumor various proteins. Each of these non-histone proteins are involved in chromatin remodeling, cell cycle regulation, and apoptosis, which all play a role in cancer etiology when dysregulated (Mariadason, 2008).

HDACs are assigned to a specific class (I-IV) depending on their homology to a particular component of yeast (Ho, et. al, 2009). The different HDACs of each of the four classes have specific functions and regulate various cellular processes. Class I HDACs are ubiquitously expressed and are typically located in nucleus. Class II HDACs are tissue-specific, and can be found in either the nucleus or cytoplasm. Class III and IV HDACs are not of particular interest in this aspect of research, although they do also possess important functions in gene regulation. Class I and II histone deacetylases regulate gene expression in multiple ways. The HDACs included in both class I and II contain specificity for certain complexes and function to repress target gene expression, while other complexes favor other functions within genes, such as induced cell cycle arrest or apoptosis (Mariadason, 2008). HDACs function to remove an acetyl group from nuclear histones, which leaves the histone positively charged. The now positively charged histone then has an increased affinity for negatively charged DNA, which results in the repression of transcription, leaving DNA transcriptionally inactive. Another mechanism by which HDACs function is the catalysis of transcription factors that possess sequence-specific,

DNA binding properties. Ultimately, the role of acetylation and deacetylation of histones is to enhance or repress transcription by increasing or decreasing the binding action of DNA. These roles of Class I and II HDAC in normal colon and in colon cancer were reported in a review article, *HDACs and HDAC inhibitors in colon cancer,* by John M. Mariadason (2008). Mariadason also states that in normal, noncancerous colons, class I and II HDACs function to maintain cell proliferation and survival, while also inhibiting differentiation.

Class I HDACs have been studied for their role and functions within colon cancer cells as well as their role in normal colon cells (Ropero & Esteller, 2007). These HDACs have two mechanisms by which they can disrupt gene expression. They may be recruited by specific transcription factors to the promotor region of p21, which is a tumor suppressor gene. After recruitment, the HDACs can repress transcription of the p21 gene by deacetylation, causing it to become transcriptionally inactive. The second mechanism by which Class I HDACs have been thought to function is by binding to the transcription factors themselves, causing them to switch from transcription activators to transcription repressors. Through each of these mechanisms, transcription is repressed via indirect deacetylation or the direct binding of HDACs to transcription factors. The role of class II HDACs has not yet been researched in depth, however, both class I and II have been shown to suppress the p21 gene via various mechanisms. Class III HDACs have been shown to possess properties for regulating energy metabolism, stress response, DNA repair mechanisms, apoptosis or deterioration of cells, and deacetylation. Class I, II, and III HDACs promote cancer promotion or progression via various mechanisms, which leads to the interest in HDAC inhibitors in cancer prevention and treatment (Mariadason, 2008).

HDAC Inhibitors

A specific area of interest within epigenetics and chemoprevention is the role of histone deacetylase (HDAC) inhibitors (Ho et.al, 2009). HDAC inhibitors (HDACi) function to prevent HDAC from the deacetylation of histones, thereby, restoring DNAs transcriptional activity. Histone deacetylation inhibitors (HDACi) have become a prime area of focus for chemoprevention, due to their suppression of HDAC functions. HDACi function to suppress or limit the dysregulation of genes in cancer and other chronic diseases. Research has shifted towards investigating dietary components that may possess these same characteristics and function similarly to HDACi, which results in beneficial chemopreventative properties. There are two main mechanisms by which dietary components, or isolated phytochemicals, carry out their functions similar to HDACi (Bisson et.al, 2011). One mechanism by which isolated phytochemicals can have chemotherapeutic properties is by acting as competitive inhibitors by binding directly to the catalytic site of HDAC. The second mechanism is the act of allosteric inhibitors in which they bind to allosteric sites that are critical for interacting with other proteins. Through both of these main mechanisms, isolated phytochemicals as part of the diet are able to function similarly to HDAC inhibitors.

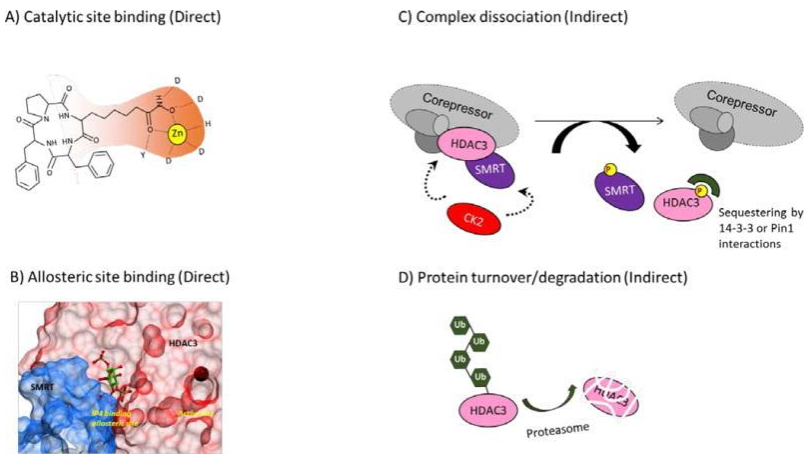

Figure 3. (Bisson, Lohr, Williams, Dashwood, & Rajendran, 2016. Histone and Non-Histone Targets of Dietary Deacetylase Inhibitors).

Dietary Components

Various dietary components have been studied for their chemotherapeutic properties due to their functional similarity to HDAC inhibitors (Ho et.al, 2009). The similarity in functions of HDAC inhibitors and particular dietary components is due to the similarity of their structure, which allows them to competitively or allosterically inhibit HDACs. Small chain fatty acids, which are the end result of fermentation of dietary fiber, function as HDAC inhibitors by also inhibiting cell proliferation, inducing apoptosis in cancer cells, activating tumor suppressor genes such as p53, and increasing histone acetylation (Roderick, et. al, 2006). All of these mechanisms which small chain fatty acids act are in opposition to the role of HDACs, support HDAC inhibition. Another component of the diet that possesses HDAC inhibitor properties is isothiocyanates (ITC), which can be consumed via cruciferous vegetables such as broccoli, cauliflower, cabbage, kale, and other related vegetables. These foods containing isothiocyanates play a role in inhibiting HDACs from performing deacetylation in cancer cells, therefore, resulting in increased acetylation. (Dashwood & Ho, 2008).

Cell-cycle arrest

Many dietary components that function similarly to HDAC inhibitors have been shown to induce cell-cycle arrest and apoptosis in damaged, or cancerous, cells (Rajendran et.al, 2011). The cell cycle undergoes four stages: G1, S, G2, and M. G1 is the phase in which the cell-cycle begins. The S phase is where replication of DNA takes place, as the cell prepares to divide. The G2 phase continues to prepare the cell to divide, and, finally, the M phase is where mitosis takes place. During this cell cycle, there are checkpoints which serve as regulatory DNA sensors. Checkpoints function to check cells for DNA damage, growth factors, nutrients, cell size, and other normal cell characteristics (Chen & Kong, 2005). There are checkpoints at each phase of

the cell-cycle, and they determine if the cell is permitted to continue to the next phase. When a cell becomes damaged, or unfit to move onto the next phase, it will become "arrested" in that phase until repair mechanisms fix it or it undergoes apoptosis (Alberts, et al, 2008). The cell cycle is of important interest to the dietary components that function similar to HDAC inhibitors because many of them induce cell-cycle arrest and apoptosis.

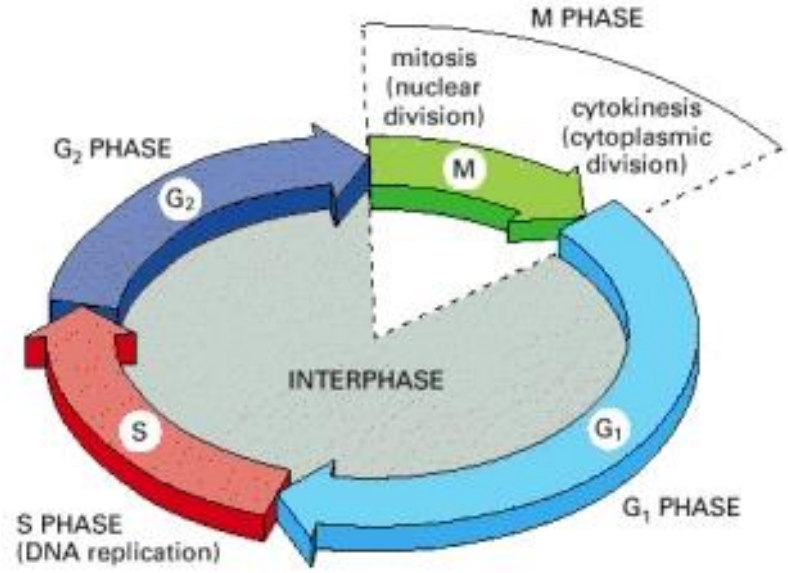

Figure 4. (Alberts, Johnson, & Lewis, 2002. An Overview of the Cell).

Specific components of the isothiocyanate group have been studied in order to better understand what exactly is producing chemotherapeutic properties in certain foods (Ho et.al, 2009). Compounds of interest include benzyl-isothiocyanate (BITC), sulforophane (SFN), phenethyl-isothiocyanate (PEITC), phenylhexyl isothiocyanate (PHITC), allyl-isothiocyanate (AITC), and various other long chain ITCs. Benzyl-isothiocyanate (BITC) has been shown to induce cell cycle arrest, activate the tumor suppressor gene p21, and increase acetylation of histones (Jeong & Kong, 2005). Sulforophane (SFN), another dietary component of cruciferous vegetables, exhibits important chemotherapeutic properties such as induced DNA damage in cancer cells, reduced HDAC activity, increased acetylation of histones, and inhibition of tumor

growth. Phenethyl-isothiocyanate (PEITC) functions to demethylate promoter regions and alter chromatin states, which both lead to dysregulation of gene expression and eventual death of cancer cells. Phenylhexyl isothiocyanate (PHITC) is a compound capable of affecting the promoter region of chromatin in cancer cells. Allyl-isothiocyanates (AITC) function in chemoprevention via mechanisms that induce apoptosis and cell-cycle arrest in certain cancer cells. Although each of these compounds in isothiocyanates work synergistically to inhibit HDAC activity, their mechanisms for doing so vary. (Royston & Tollefsbol, 2015).

BITC

One component of isothiocyanates is benzyl-isothiocyanate (BITC), which possesses chemotherapeutic characteristics and preventative mechanisms. BITC has been shown to cause an upregulation of G2/M phase cell-cycle arrest and eventual apoptosis of the cell (Duval, et. al, 2016). The two fates of cells that undergo G2/M phase arrest are cell death or severe DNA damage that will eventually lead to apoptosis. Not only does BITC function to arrest cell-cycle in the G2/M phase, it also modulates the regulatory proteins for that phase as well. In a laboratory-based study with rats, it was shown that BITC exposure in smaller doses led to a decrease in cell growth due to the increase in cell-cycle arrest when compared to the control group (Singh, 2012). Larger doses, however, showed decreased cell growth as well as increased apoptosis, therefore, leading to an overall larger decrease in cancer cells when compared to the control group. This shows the irreversible effects of BITC on both cell-cycle arrest as well as apoptosis induction. In addition to BITC's ability to induce apoptosis and cell-cycle arrest in certain cancer cells, it has also shown to induct tumor suppressor gene, p21. This action extends the impact made on the prevention of cancer promotion and progression through benzyl-isothiocyanates found in cruciferous vegetables (Chen & Kong, 2005).

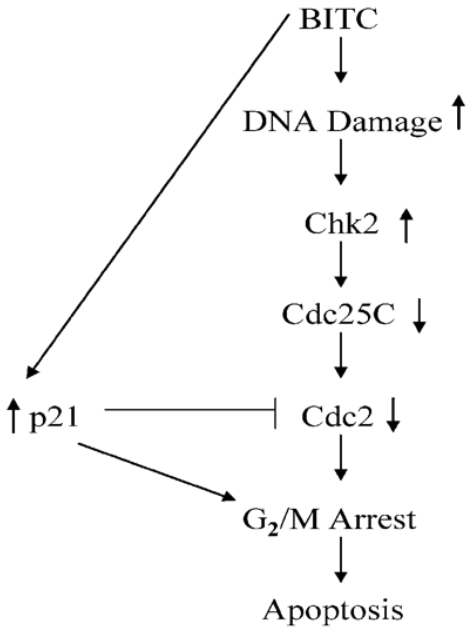

Figure 5. (Lau, Chen, & Wong, 2010. Allyl isothiocyanate induces G2/M arrest in human colorectal adenocarcinoma).

PEITC and SFN

Isothiocyanate compounds of particular interest in the review article, *Molecular Targets of Dietary Phenethyl Isothiocyanate and Sulforaphane for Cancer Chemoprevention*, are sulforophane (SFN) and phenethyl-isothiocyanate (PEITC) (Kim et.al, 2016). Both of these compounds interact with the Nuclear Factor Kappa Beta (NFkB) inflammatory pathway. The NFkB inflammatory pathway causes an increase in pro-inflammatory cytokines, anti-apoptotic genes, and other factors that contribute to an increased risk of chronic disease development. PEITC plays a role in inhibiting the inflammatory response of the NFkB pathway by stabilizing nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha, or IkBalpha, which sequesters NFkB in the nucleus, preventing it from initiating the inflammation cascade. PEITC and SFN also have similar mechanisms by which they both inhibit the phosphorylation of IkBalpha. Inhibition of inflammatory responses plays an important role in the prevention of cancer progression due to the role inflammation plays as a risk factor for developing cancer. SFN decreases the binding affinity for NFkB via two main mechanisms: direct and indirect binding

(Cheung & Kong, 2009). The direct binding of SFN to NFkB happens via the thiol group, which leads to the decrease in binding ability of NFkB. The indirect mechanism takes place via redox regulators of NFkB. Both of these mechanisms lead to NFkB's decreased ability to bind, and, therefore, inhibits the inflammatory response (Cheung & Kong, 2010).

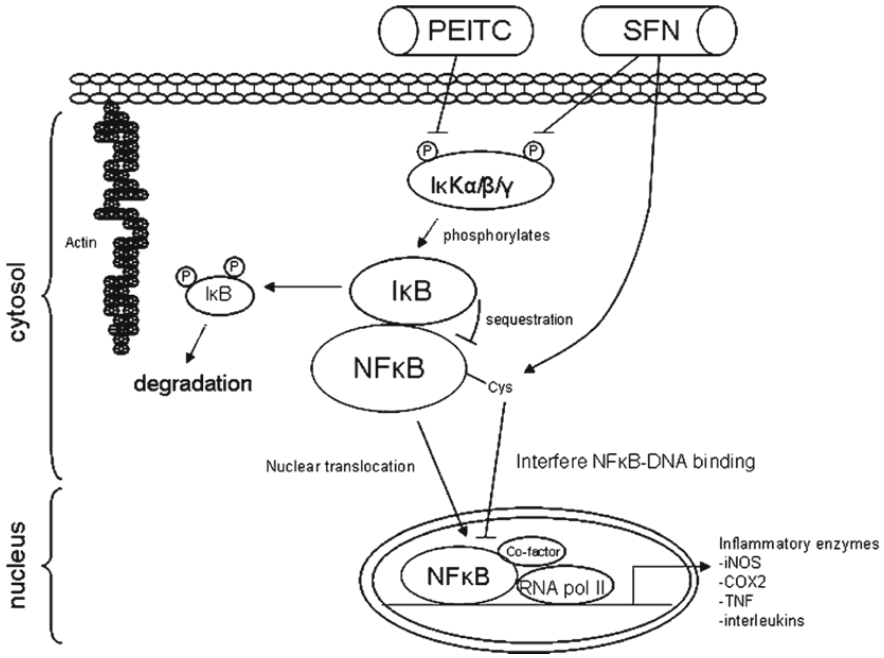

Figure 5. (Myzak, M., Ho, E., & Dashwood, R. 2006. Dietary agents as HDACi).

PEITC and SFN play important roles in the decrease in cancer progression via common mechanisms including induced apoptosis and cell-cycle arrest (Cheung et. al, 2009). Apoptosis has been predicted to be induced by SFN through reactive oxygen species (ROS). ROS begin the apoptotic response by causing dysregulation of the mitochondria, which causes the release of cytochrome c, which then causes programmed cell death or apoptosis. PEITC has been shown to bind to tubulin within cells which then causes apoptosis with a higher potency than SFN. Cell cycle arrest, another common mechanism by which compounds prevent cancer progression, can be induced by PEITC and SFN via similar mechanisms. Exposure to each of these compounds for three, six, and twelve hours was recorded in vivo (Cheung et. al, 2009). Three hours of

exposure to PEITC resulted in a significant decrease in growth of all types of cancer cells. Six and twelve-hour exposure to SFN resulted in time-dependent cell-cycle arrest and irreversible apoptosis. The six-hour exposure to SFN showed reversible mechanisms, however, the twelve-hour exposure had more long-lasting effects of cell-cycle arrest and apoptosis. These two isothiocyanate compounds have significant impact on the progression of cancer cells via various mechanisms and provide promising evidence for future prevention of cancer through dietary components (Chen & Kong, 2005).

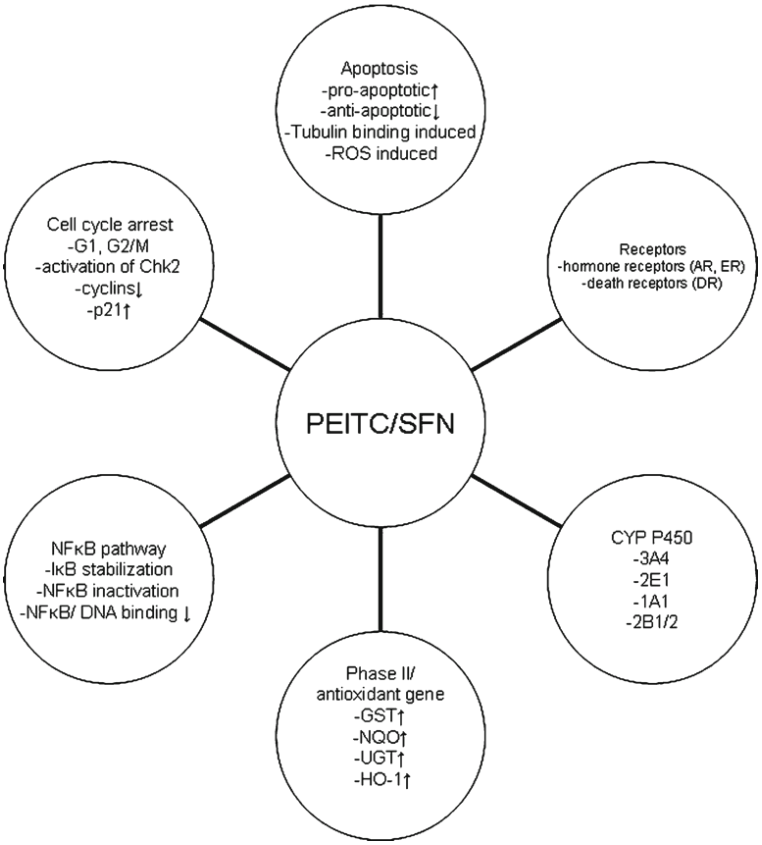

Figure 7. (Myzak, Ho, & Dashwood, 2006. Dietary agents as histone deacetylase inhibitors).

AITC

Allyl-isothiocyanate (AITC), another compound in isothiocyanates consumed through cruciferous vegetables, also possesses qualities of chemoprevention (Lau, Chen, & Wong, 2010). AITC has been shown to induce apoptosis in liver cancer cells, as well as, increase cell-cycle arrest and the production of reactive oxygen species (ROS), which can eventually lead to

apoptosis as well. Although AITC, and other compounds of isothiocyanates, function in chemoprevention, each component does so via various mechanisms. AITC, specifically, functions to induce cell-cycle arrest by treating liver cancer cells in mice with 2 to 5 microliters for a 72-hour time period. Conclusions of the study include inhibited cell proliferation and increased apoptosis of cells. AITC also increased the production of reactive oxygen species via oxidative damage, which then led to an increase in the death of liver cancer cells. Each mechanism of isothiocyanates, whether it be apoptosis, cell-cycle arrest, increased ROS production, or any other action that induces cell death or inhibits cell growth, has an important role in chemoprevention. This can all be accomplished through eating cruciferous vegetables, which continues to prove the importance of nutrition in the prevention of chronic diseases. (Duval, et. al, 2016).

Cyanohydroxybutene and Glutathione

An area of heavy focus within chemoprevention is the role of glutathione (GSH), a naturally occurring protein in many cells (Circu & Aw, 2011). GSH has been studied for chemopreventive properties and its relationship with dietary components such as cyanohydroxybutene (CHB), which is found in cruciferous vegetables. CHB has been studied for its ability to activate GSH production in the body. Glutathione plays important roles in maintaining the integrity of cells within the body, with its functions including: anti-oxidative mechanisms, modulation of immune responses, and cell detoxification and pro-oxidation. According to Balendiran, Dabur, and Fraser, each of these anti-cancer properties of GSH play a role in cancer prevention (Balendiran, Dabur, & Fraser, 2004). However, elevated levels of GSH can actually prevent chemotherapeutic drugs from treating cancer. Therefore, glutathione has been shown to be essential in cells in order to maintain proper function, but should not reach

elevated levels if an individual has already developed cancer. The important question remains: What is the appropriate amount, where the balance between helpful and harmful is most beneficial? Researchers have attempted in vivo experiments that reverse the effects of elevated levels of GSH in order to restore sensitivity to chemotherapy drugs. Two examples of this in *Glutathione and Cancer* are OTZ and BSO (Balendiran, et. al, 2004). OTZ, oxothiazolidine-4-carboxylate, monitors levels of GSH within cells, while BSO, buthionine sulfoximine, functions to prevent further GSH synthesis. These experiments were carried out by altering GSH levels via administering certain amounts of OTZ and BSO, followed by administration of certain chemotherapy drugs. The response to the chemo drugs, as well as the levels of GSH, was then analyzed and compared. OTZ treatment resulted in lower levels of GSH and an increased sensitivity to chemotherapy drugs. BSO resulted in an increased sensitivity to some chemotherapy drugs, but a decrease to others. An increase in toxicity of the cell was also reported in cells treated with BSO, most likely due to the increased levels of GSH. Glutathione carries out many important functions in the body, however, the research that has been conducted on GSH and its role in cancer is one of complexity. Elevated levels of GSH have been shown to increase protection of cancer cells through decreased sensitivity to chemotherapy drugs, which therefore promotes cancer progression. However, with the usage of compounds, such as the previously mentioned BSO, in combination with GSH, there is promising hope for future cancer prevention and treatment. (Balendiran, Dabur, & Fraser, 2004).

Diallyl disulfide

Diallyl disulfide, a main compound found in garlic, is another dietary component that has chemopreventative and chemotherapeutic actions through various mechanisms similar to HDAC inhibitors (Ling Hui, Li-Feng Lu, Jie He, Guo-Hua Xiao, and Hao Jiang). Diallyl disulfide

(DADS) has multiple targets for the prevention of cancer including apoptosis and cell-cycle arrest, inhibition of proliferation, migration, and invasion of cancer cells, and inhibited growth of cells both in vivo and in vitro. Induction of apoptosis occurs in the G2/M phase, but in low doses can also induce cell cycle arrest in the G0/G1 phase also (Ling, et. al, 2017). Another major mechanism that is studied in DADS ability to prevent cancer is the expression of checkpoint kinase 1 (ChK1). The important of ChK1 in the initiation of cancer is its ability to detect damages and mistakes within the DNA. These checkpoints function to find mistakes and respond by making sure that the damaged cell does not continue through the cell-cycle phases. ChK1 serves important functions in the suppression of cell growth and induction of apoptosis in cancer cells. ChK2, however, has not been shown to have the same beneficial outcomes as ChK1. DADS activate ChK1, and the overexpression has been shown to cause G2/M cell-cycle arrest through the phosphorylation of ChK1. ChK1, as a DNA repair mechanism monitor, helps maintain genomic integrity by either holding cell in its current phase until it can be repaired, or inducing apoptosis in the damaged cells. For a cell to transition from the G2 phase to mitosis, ChK1 must be deactivated. Therefore, an increase in ChK1 in mice showed an increase in G2/M phase cells. This shows that ChK1 is necessary for DADS induced cell-cycle arrest (Ling, et. al, 2014).

Diallyl trisulfide

Diallyl trisulfide is another component of garlic that functions similar to diallyl disulfide (Jiang, Zhu, Liu, Xu, Zhan, Li, Li, Cai, & Cao, 2016). Cancer prevention through consumption of garlic is due largely to diallyl trisulfides (DATS) and diallyl disulfides (DADS), which are important preventative and therapeutic components. DATS express these properties via various mechanisms that lead to increased reactive oxygen species (ROS) production, decreased blood

pressure and cholesterol, or increased aggregation of platelets. The overall effect of DATS on cancer cells is primarily apoptosis and decreased cell proliferation. DATS, not only protect against cancer promotion and progression, but also guards against cardiovascular diseases via anti-inflammatory and antioxidant properties. Whenever DATS are metabolized in the body, by glutathione, they then form hydrogen sulfide, which has anti-inflammatory and antioxidant properties. These properties of DATS are important in chemoprevention and prevention of other chronic diseases (Jiang, et. al, 2017).

Allyl Mercaptan

Allyl mercaptan (AM) is an organosulfur compound found in garlic that functions as a dietary histone deacetylase inhibitor (HDACi) (Oi, Kawada, Shishido, Wada, Kominato, Nishimura, Ariga, & Iwai, 1998). Among the organosulfur compounds in the diet, AM has been shown to be of the most potent in the role of cancer prevention. AM has been studied in vivo for its chemopreventative effects, with experiments focusing on cell cycle arrest and apoptosis of cancer cells. AM experiments showed that it possesses anti-proliferative and hyperacetylation of cancer cells. Hyperacetylation of cells via AM has been linked to activation of p21, a tumor suppressor gene, which is repressed by HDACs. By activating p21, there was a reported subsequent increase in binding of p53, another tumor suppressor gene. Both p21 and p53 function synergistically to suppress cancer and tumor growth. Another mechanism by which AM prevents cancer cells is by acting as a competitive inhibitor of HDAC. These functions of AM have been shown to result in cell-cycle arrest and eventual apoptosis of cancer cells. Whenever AM was administered at ~20 micro molar, there was a resulting 50% decrease in HDAC activity, which supports the hypothesis that AM acts similarly to HDAC inhibitors (Nian, Delage, Pinto, & Dashwood, 2008).

Limitations

Nutrition has been and always will be of the utmost importance in maintaining a healthy lifestyle, and has also been proved to aid in the prevention of chronic diseases such as cardiovascular disease, type II diabetes, cancer, and other inflammatory diseases. (Hernandez & Chien, 2015). Cruciferous vegetables and garlic are shown to be inversely related to the risk of certain cancers, such as breast, lung, colorectal, and prostate. However, an area of research, which appears to still be in its infancy, is the amount of consumption necessary for each of these previously mentioned dietary factors to provide these beneficial chemopreventative properties. A common question includes: "How much would I need to eat in order to benefit from the positive effects these foods offer," and this is a valid inquiry. As researchers attempt to understand the amount of isothiocyanates people with or without cancer have been exposed to, there are many factors to consider which make that difficult (Hernandez & Chien, 2015). The bioavailability and chemical digestion/metabolism processes of cruciferous vegetables, for example, are areas of interest in the field of nutrition and chemoprevention. Some research studies have focused on measuring the amount of isothiocyanates excreted via urine, but it still remains difficult to understand exactly how much is actually put to use in the body through cruciferous vegetable intake. While many organizations have recommended dietary intakes for vegetables, there are few recommendations solely focused on cruciferous vegetables. According to Higdon et. al, individuals should aim for at least 5 servings of cruciferous vegetables per week.

Conclusion

Chemotherapy is a common and, for most cases, successful treatment for cancer (The American Cancer Society medical and editorial content team, 2016). However, accompanying this treatment, both during and after, are harmful side effects. Researchers continue to search for

new treatments, and hopeful cures, for this chronic disease which affects millions each year. Exploring every aspect of potential treatment, many research studies have focused on the effects of various foods and their beneficial properties and potential roles in chemoprevention of certain tumors. Through such research, chemopreventative properties have been attributed to phytochemicals in various fruits, vegetables, and other plants. Of specific interest in this paper are garlic and cruciferous vegetables, such as broccoli, cabbage, cauliflower, and brussel sprouts. Such epigenetic research includes the study of histone acetylation (HATs), histone deacetylation (HDACs), and histone deacetylase inhibitors (HDACi). The role of each of these is to either activate or deactivate the transcription of DNA via histone acetylation, deacetylation, or the inhibition of deacetylation. The tightly kept balance between the acetylation and deacetylation of histones has been examined and analyzed for the role in preventative properties against cancer cell progression (Kim et. al, 2016). Potential beneficial roles of chemoprevention have been attributed to HDAC inhibitors, and the similarity of these dietary components to HDAC inhibitors has been a subject of heavy focus within epigenetic research. The role of HDAC inhibitors has provided promising hope for the future of chemoprevention, and provided insight into dietary components and their beneficial effects. Via numerous mechanisms, many of these dietary components have in common the ability to induce cell-cycle arrest and apoptosis in cancer cells. In addition to cell-cycle arrest and apoptosis of cancer cells, these components of cruciferous vegetables and garlic have numerous other beneficial properties including anti-inflammation, decreased tumor invasion, and anti-viral and anti-bacterial effects (Hernandez & Chien, 2016). The mechanisms by which these components of cruciferous vegetables and garlic act have been shown to positively impact chemoprevention, and provide promising information for the future of cancer prevention and potential treatments.

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