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Therapeutic Potential of Dietary Polyphenols

Amy L. Stockert and Seth Hall

Abstract

The chapter summarizes available research on polyphenols and the potential for polyphenol based therapeutics. Polyphenols have the potential to be used in a multi-target fashion therapeutically. The majority of the polyphenol benefits appear to share positive effects across multiple disease states including inflammatory diseases, diseases of metabolic dysregulation and cancer. The reviewed literature includes human, animal and cell culture based studies. Selected mechanisms within each disease state are highlighted including interleukin inflammatory markers, NF- κ B, acetyl-CoA concentration regulation of metabolism, and p-glycoprotein multidrug efflux pump associated with cancer treatment failures. Reviewed studies discuss polyphenols inhibiting transcription factors that control expression on inflammatory factors as well as activating other transcription factors that increase expression of enzymes protective of oxidative damage. Levels of metabolic regulatory enzymes are also affected positively by polyphenol addition through epigenetic modifications. Epigenetic modifications affecting cancer development and progression appear positively affected by polyphenol treatment. Additionally, oxidative damage protection of normal cells can be achieved by polyphenol treatment thus limiting chemotherapeutic damage. Upon review of the available literature, a strong case for the potential use of polyphenols in therapeutic situations stands out. Potential risks included are that the purity and specific concentrations required to achieve therapeutic benefits without potential side effects need to be examined prior to the adoption of therapeutics.

Keywords: polyphenols, therapy, natural products

1. Introduction

Polyphenols are molecules with multiple hydroxyl groups that have been shown to provide numerous health benefits including reduction of inflammation, metabolic control and anti-cancer properties. Polyphenols can be found in a variety of natural sources such as cinnamon, green tea, coffee, vegetables and fruits. Although some evidence exists for the mechanisms of polyphenol molecules that lead to these health benefits, there is still much unknown about how these compounds act to alter metabolism, inflammation levels and cancer pathways. Some research suggests epigenetic modifications that alter expression level of disease state genes explain the benefits, while others identify potential signaling pathway and transcription factor targets affected by polyphenols or their metabolites as the method of control. One difficulty in researching the potential for polyphenol based therapies is the tremendous crossover between pathways that can affect multiple metabolic actions

ranging from dysregulation of metabolism to loss of cell cycle control. On top of the multi-targeted effects from signaling, epigenetic modifications can be detected and identified but not always possible to predict. Although the field of dietary therapeutics provides a much needed alternative to many other treatments, the uncertainty of use in certain cultures make it a challenging research topic but all the more important to tackle.

Some of the most commonly studied polyphenols include the catechin group. Available evidence suggests that some forms have higher activity on some targets but the active forms differ from target to target. For example, it has been suggested that resveratrol, which is a fused ring complex between two catechin molecules, binds to and modulates the allosteric effects of Sirt1 thus playing a role in deacetylation/acetylation of multiple targets [1–3]. The metabolic regulator FoxO1 is a transcription factor that is deacetylated by Sirt1 thus changing metabolic function as well as cell death pathways [4]. Modified catechins known as epigallocatechin gallate (EGCG) are found in high levels in green tea and have been shown to modify the epigenome of MCF7 breast cancer cells [5]. Observed results show multiple types of epigenetic modifications including both methylation of the DNA and acetylation of histones. Compounds found in cinnamon include polyphenol A, a linked dual catechin, which has been studied as a potential insulin mimic compound [5]. Additional compounds found in cinnamon include rutin, an acid labile bond between quercetin and epicatechin that have been predicted to interact with Sirt1 [1]. Additionally cinnamon has been shown to increase expression of both GLUT4 expression and translocation in adipose and muscle, although the responsible component of cinnamon has not been identified with certainty [6, 7].

The collection of evidence suggesting that natural products provide profound therapeutic benefits is growing. Although pharmaceutical industries have developed drugs that are effective at treating symptoms of metabolic dysregulation and inflammation, the majority of these medicines are focused on symptom management and targeted effects. The spectrum of benefits that are possible with polyphenol based therapies offer a potential to treat multiple disease states by targeting the root cause of disease. There is still much to be learned about how the effects of polyphenols can be predicted and if cross reactivity exists that could benefit one disease state but hurt another. However, the likelihood of reciprocal effects of a therapeutic is less likely when one known effect is beneficial on a broad scale than if the polyphenol therapy were aimed at controlling only one target. As many people become concerned about potential side effects of pharmaceuticals, some find comfort in alternative medicine such as polyphenols.

2. Effects of inflammation

Recent literature has demonstrated that a growing number of disease states result from chronic inflammation [8]. Inflammation is the body's response to a variety of stimuli such as viral or bacterial infection, disease state markers, and injury resulting in tissue damage. The body has developed and refined this inflammatory response as an immune response to protect the body from damage from these stimuli. In general, an individual's immune response is elicited only as a result of the stimulus. This specific response may cause an acute inflammatory response of increased inflammatory markers which generally function to protect the body for a short period of time, but then return to normal levels. Acute inflammation, although potentially serious in some cases, can be expected to alleviate over time. In contrast, chronic inflammation is the type of inflammation that is typically associated with disease states or development of disease. Chronic inflammation is an

ongoing, constant and consistent release of inflammatory markers that ultimately result in damage to the tissues. In many cases, chronic inflammation results from obesity, continuous stress or anxiety, diabetes, and poor sleep. Autoimmune conditions can result from chronic inflammation, or can themselves add to the chronic level of inflammatory proteins circulating in the body. Oftentimes this is a whole body inflammatory response rather than an isolated location or injury as seen in acute inflammation.

2.1 Why is inflammation a health issue?

Although it appears to have taken decades to confirm the involvement of inflammation in disease risk, it seems to be a logical expectation. Inflammatory markers in circulation are chemokines that direct the body's processes. They exist simply to allow the body to detect a problem and illicit a response. Inflammation represents one of our most innate protective responses. However, it stands to reason that if the body detects a damage risk, the response will be elevated. This elevated inflammatory marker level itself can result in damage that increases the response further. The inflammatory response becomes chronic and continues in a feed forward loop continually signaling the body to respond. The effects of this endless response cycle result in disease state symptoms that require therapeutic intervention. In a similar fashion, tissue damage resulting from chronic inflammation can result in the development of diseases of metabolic dysfunction, asthma, cardiovascular disease, cancer, arthritis, among others.

It has become more common to exist in a continuous loop of stressors. Some of these stressors include: malnutrition, chronic stress, obesity, inactivity, and toxin exposure. All of these conditions can lead to chronic inflammation and result in further tissue and cell damage. Although a healthy lifestyle can certainly help to alleviate these responses, sometimes the disease state itself makes achieving the ideal healthy lifestyle nearly impossible. Careful attention to the type of foods selected can help decrease the chronic inflammation and break the continuous cycle. Certain foods and spices contain high levels of polyphenols which have been shown to help mediate the inflammatory process. Visceral obesity in particular can increase inflammation and associated markers including reactive oxygen species, interleukins 6 and 8, adiponectin and tumor necrosis factor alpha (TNF- α) [9, 10].

2.2 How can polyphenols limit inflammation?

There are several potential ways in which polyphenols can help to moderate the inflammation levels: these include targets in the signaling pathways, limitation of reactive oxygen species and reactive nitrogen species. Once generated the reaction oxygen or nitrogen species can result in reactive organic molecules as well. These reactive compounds can cause damage to the cells' genetic material, lipids found throughout the body especially in cell membranes and proteins required for cell structure and repair [11, 12].

Polyphenols show considerable potential to regulate oxidative stress and therefore inhibit inflammation [13–15]. Reactive oxygen species (ROS) are generated readily by metabolic reactions and include hydrogen peroxide, superoxide and hydroxyl radicals. These ROS can be particularly troublesome when they interact with nitric oxide in the blood vessels because nitrogen reactive species peroxynitrite is produced. Similarly, ROS and lipids circulating in the arteries can react to form oxidized lipid which can worsen the development of atherosclerosis. Some polyphenols, such as flavonoids, have the ability to scavenge superoxide and peroxynitrite thus inactivating them and preventing the almost certain cell damage [16].

In addition to inactivating ROS and peroxynitrite, some polyphenols also chelate the metal ions required for creation of these reactive species thus inhibiting their activation [17].

Several studies have identified signaling protein and transcription factor targets that can be affected by polyphenols [18–20]. In many cases the polyphenols target multiple proteins within a cascade of responses that can alter not only inflammatory response, but also mediate expression of cell death genes and metabolic function. Although initially the effect on inflammation will be discussed, there is significant overlap in signaling cascades that result in multiple effects.

Available data trends demonstrate that polyphenols are able, in part, to help regulate the expression of nucleosome factor kappa beta (NF- κ B), a transcription factor that is expressed during conditions of oxidative stress [18]. NF- κ B binds to DNA when active and functions as a positive transcription factor for a variety of pro-inflammatory cytokines. An increase in inflammation can result in increased levels of TNF- α , interleukin-6 (IL-6) and enzymes inducible nitric oxide synthase and cyclooxygenase 2. Inducible nitric oxide synthase is responsible for the production of the reactive nitrogen peroxynitrite, and cyclooxygenase 2 catalyzes the production of prostaglandins. The ability of polyphenols to interact with these factors identifies polyphenols as potentially healthful food bioactive that can help fight both the results of inflammation as well as the disease that cause inflammation. Curcumin, a polyphenol found in turmeric root, has been shown to block activation of NF- κ B, thus blocking this pathway and excluding NF- κ B from the nucleus [18]. Similarly, some polyphenols can decrease NF- κ B activity by directly interacting with subunits of the factor [21].

Some polyphenols have been found to activate the transcription factor Nrf2, which when expressed at high levels protects the cells from the damaging effects of reactive oxygen species and inflammatory markers [20, 22]. Nrf2 is a key inducer of protective mechanisms against oxidative stress, leading towards increased production of enzymes such as superoxide dismutase, catalase, and glutathione-S transferases, all of which help to modulate the ROS produced. Polyphenols have been shown to increase nuclear translocation of Nrf2, thus allowing increase transcription of the oxidative stress protective genes [22].

3. Metabolic effects

3.1 Metabolic dysregulation

The loss of proper metabolic regulation results in a variety of disease states including those associated with chronic inflammation mentioned above. Some such diseases include obesity, diabetes, hyperlipidemia, and type 2 diabetes. Patients that develop a dysregulated metabolism also tend to experience chronic inflammation and vice versa. The two health concerns feed off of each other. Metabolic dysregulation historically has been assigned to lifestyle and diet only, but more recently consideration of multigenerational epigenetic effects and environmental contributions have been included as a cause for the beginning of metabolic dysregulation [23–25]. The days of it being dismissed as caused completely by the patient are or should be past. Fetal programming has been adopted as a significant cause of metabolic syndrome in offspring that can lead to the development of obesity and insulin resistance [26–29].

Many epigenetic modifications lead to changes in metabolic function. One such example is acetyl-CoA carboxylase, the enzyme that converts acetyl-CoA into malonyl-CoA for entry into the fatty acid synthesis pathway. Galdieri and Vancura

have demonstrated that this enzyme aids in regulation of histone acetylation. Specifically they have identified that histone acetylation, one major method of epigenetic control, depends on acetyl-Co generated prior to entry into the Krebs cycle that can be limited in conditions where acetyl-CoA carboxylase is expressed at higher levels. Interestingly, they noted that the acetyl-CoA required to acetylate histones for transcriptional regulation was more readily available when expression of acetyl-Co carboxylase was limited [30].

The importance of this acetyl-CoA – histone acetylation connection is that a global connection between metabolic activity and the transcriptional control of all genes. Any upregulation in the acetyl-CoA carboxylase, which you would expect in individuals with excessive glucose intake due to either limited balanced meal options or overindulgence in high carbohydrate foods, could potentially be inhibiting their ability to acetylate histones. Additional enzymes that contribute to the intercellular concentration of acetyl-CoA, such as ATP citrate lyase have also been identified [31]. ATP citrate lyase converts citrate formed in the first step of the Krebs cycle to acetyl-CoA. Again this further demonstrates how food intake and availability can be communicated to cells in such a way that allows gene transcription to be silenced or enhanced.

Histone acetylation is catalyzed by histone acetyl transferases (HATs) and responsible for reprogramming gene expression along with histone deacetylases (HDACs). In general acetylation of histones in a specific gene region will increase expression of the gene, while deacetylation (catalyzed by HDACs) decreases gene expression of subsequent genes. Polyphenols have been shown to interact considerably with the HAT and HDAC enzymes and therefore have the potential to assist with re-regulation of metabolism.

3.2 Polyphenol potential for re-regulation

Numerous studies have demonstrated the potential to reverse, at least partially, some of the changes resulting from metabolic dysregulation [32–35]. Reversing or alleviating some of the inflammation associated with conditions such as metabolic syndrome may help to mediate the increased risk of cardiovascular disease with these conditions. The incidences of cardiovascular disease and diabetes are increasing globally and polyphenols offer a natural, inexpensive way to help slow the development of the comorbidities associated with these disease states. In most cases the effectiveness of the polyphenol treatment comes from its effects on insulin resistance and inflammatory reduction [32, 33, 36]. Although there seems to be significant effects on improving health with the use of dietary polyphenols, the more comorbidities a patient suffers from, the more unlikely it will benefit them to the extent necessary. For this reason, it is important that patients hoping to achieve results from polyphenol consumption begin polyphenol therapy at the first sign of metabolic dysregulation or perhaps even better, begin using polyphenols as a preventative measure. Few studies have been conducted that look at polyphenol use as an adjunctive therapy for metabolic conditions, but rather as a potential sole therapy. Similarly, the effectiveness of polyphenol therapy alone show strong ties to specific populations [34].

As discussed previously, availability of acetyl-CoA is controlled by metabolic enzymes and dietary input. Levels of acetyl-CoA also affect histone acetylation which can control transcription of a variety of genes. A proposed link of HAT activity to diabetes exists because of the interaction between the HAT, glucokinase and hepatocyte nuclear factor that relates to a transcriptional change rather than a true epigenetic change [35]. The transcriptional changes come from the increase in acetylation marks present because of the HAT activity that interacts with the

gene promoter for pro-inflammation gene products that depend also on NF- κ B for expression [35]. This example demonstrates yet another link between diseases of metabolic dysregulation and those of inflammation or cancer.

In terms of therapeutic potential of polyphenol for metabolic dysregulation, it seems that enhancing acetylation of histones is not the only benefit of consumption. Polyphenols, particularly those found in cinnamon, improve insulin resistance and improve lipid profile [32, 33, 37, 38]. Some clinical studies have demonstrated reductions of 12.9–52.2 mg/dL in blood glucose levels while others have found less robust and potentially null effects [38–40].

4. Cancer prevention possibilities

Polyphenols likely have many different mechanisms of how they can prevent proliferation and overall survival of cancerous cells. As mentioned in previous sections, there is substantial overlap among mechanisms. Due to this overlap, it is almost certain that multiple mechanisms are involved to provide the cancer prevention properties of polyphenols. It is therefore more convenient to present research based on some of the individual actions of polyphenols such as anti-oxidative properties, pro-oxidant activity, mediation of cellular signaling, and epigenetic modifications [41].

4.1 Antioxidant properties

The structure of polyphenols makes them great antioxidants due to the high availability of hydroxyl groups attached. The more hydroxyl groups present on the molecule, the greater the potential for antioxidant activity [41]. Cancer cells have been shown to increase greater amounts of reactive oxygen species (ROS) than non-cancerous cells. Through various different pathways, ROS have been shown to promote both tumorigenesis and the proliferation through mechanisms such as angiogenesis and the promotion of cell migration [42]. Flavonoids have been shown to lower the amount of ROS by scavenging free radicals, chelating of transition metals that help form further ROS, and regulating oxidative stress-mediated enzyme activity [43]. Research has shown that rats treated with epigallocatechin gallate (EGCG) had increased levels of antioxidant enzymes [44]. Lowering ROS levels results in the prevention of cancerous cells to undergo proliferation or migration.

4.2 Pro-oxidant activity

Effectiveness of cancer treatment can also be improved by modulating oxidative levels in the cells. Oxidative stress can damage cells and cancer cells have an increased capacity to handle oxidative damage. Taking advantage of this increased capacity, cancer cells can somewhat be recognized more specifically. Therapies involving polyphenols generally reduce oxidative damage, but in cancer cells the standard signaling is already modified, thus some polyphenols actually increase oxidative damage to a level in which apoptosis and therapeutic sensitivity increased. Research shows that cancer cells undergo changes to better handle the high levels of ROS in their environment such as generating higher levels of nicotinamide adenine dinucleotide phosphate (NADPH) [45–47]. This better equips cancerous cells to resist the effects of oxidative stress that can lead to apoptosis. However, this resistance is still able to be overcome by increasing the amount of ROS to a level more than the cells can handle.

Many polyphenols have been shown *in vitro* to have pro-oxidant activity by utilizing transition metals already present in biological systems to create more ROS and overcome the natural resistance that cancerous cells possess [48–50]. Vitamin C has been shown in high doses to inhibit tumor growth as well as metastasis without harming non-cancerous cells present. Ascorbate as a standalone treatment has been shown to reduce both tumor growth and weight by 41–53% in Ovcar5, Pan02, and 9 L tumors. It was also shown to reduce the amount of metastases that were present in approximately 30% of 9 L glioblastoma control groups [51]. This shows promise, as a difficulty surrounding cancer treatment is the incidental harm of non-cancerous cells simultaneous to cancerous cells. Potentially utilizing natural polyphenols already present in biological systems may be a way to work around this issue. Another class of polyphenols, hydroxycinnamic acids, has shown the ability to damage DNA molecules in the presence of Cu(II) ions [52]. Further studies are crucial in determining the *in vivo* ability of polyphenols to replicate results shown *in vitro*.

4.3 Mediation of cellular signaling

As mentioned in both the inflammation and metabolism sections, NF- κ B is an important component in the inflammatory nature of cancerous cells. It is believed that it is the primary factor responsible for inducing a variety of cancer molecules such as adhesion molecules, growth factors, angiogenic proteins, cell proliferation proteins and inflammatory cytokines [41]. NF- κ B also increases expression of inhibitors of apoptosis and suppresses the expression of genes involved in cell death [53]. Research has shown that polyphenols have the ability to interfere with NF- κ B's mechanisms specifically involved with cancer. Flavonoids disrupt inhibitors of kappa kinase (IKK), an activator of NF- κ B, as well as binding directly to NF- κ B and preventing its binding to DNA [41, 54, 55]. The mediation of polyphenols in these pathways can provide valuable anti-inflammatory benefits that can both prevent the formation of cancerous cells and tumors, as well as removing the suppression of apoptosis that is caused by NF- κ B leading to cell death.

4.4 Epigenetic modifications

Methylation of specific cancer genes has become a key predictor of both markers of cancer and cancer survival. One example of this is the methylation state of the BRCA1 promoter gene in ovarian cancer. Research showed that patients with a higher level of methylation on the gene, had a shorter median for disease free interval. It also showed that facilitating demethylation of the gene results in increased survival time and decreased occurrence rate [41, 56]. DNA methyltransferase (DNMT) is the enzyme responsible for methylation of genes. Polyphenols have been shown to decrease methylation by inhibiting DNMT. *In vitro*, DNMT was inhibited by EGCG at a concentration of 20 μ mol/L [57]. The ability for polyphenols to inhibit DNMT and other methyltransferase enzymes makes them of interest for not only cancer prevention, but other disease states that are affected by an increase in methylation of DNA [41]. Research in this area should continue so a greater understanding of the ability for polyphenols to affect methyltransferase enzymes such as DNMT.

4.5 Cancer treatment adjunctive therapy

Cancer therapies are an ever changing area of interest as we better understand ways to induce cancer cell death as well as maintain the health of non-cancerous

cells in the body. Resistance to chemotherapies is also an area of concern making it difficult to achieve appropriate therapy and leading to more aggressive treatments which leads to an increase in harm to non-cancerous cells. One of the ways that cancer cells present resistance is in the increase of the multidrug resistant p-glycoprotein transporter. The p-glycoprotein transporter pumps the drugs out of the therapeutic intracellular location. Curcumin has been shown to suppress the action of the multidrug resistant p-glycoprotein transporter. Sulfasalazine, a specific substrate for the multidrug resistance protein ABCG2, was shown to have an increased C_{max} concentration in the presence of a 400 mg/kg dose in mice. The change was 1230 ng/mL in the absence of curcumin and 3350 ng/mL with curcumin present [58]. This would in turn result in an increase in concentration of medication inside the cancer cell and therefore greater efficacy of the therapy making curcumin a good possibility for adjuvant therapy. Another issue arises during chemotherapy in the possible need to increase ROS to produce apoptosis of cancerous cells [59]. These ROS also negatively affect non-cancerous cells so the need to protect these cells is crucial to ensure appropriate chemotherapy can continue. As mentioned above, one of the mechanisms in how polyphenols can prevent cancer is through their antioxidant activity. Through this mechanism, polyphenols can provide valuable adjuvant therapy for patients allowing them to prolong their chemotherapy without increasing negative effects associated with the increase in ROS.

5. Conclusion

The potential for polyphenols to be used therapeutically appears more probable as more research is completed. Additionally, the benefits likely cross into multiple disease states with positive effects for them all. Pro-inflammatory transcription factor NF- κ B is inhibited by binding of polyphenols, thus limiting the expression of harmful inflammatory factors. Similarly, NF- κ B activity can also be blocked by limiting its activation via the signaling pathway. While limiting NF- κ B activity limits inflammation, activating the positive transcription factor Nrf2 increases expression of enzymes protective of oxidative damage. Studies demonstrate that polyphenols activate Nrf2.

From a metabolic perspective, limiting inflammation is also ideal, thus overlapping benefits are observed from the anti-inflammatory effects described when considering metabolic dysfunction. Limitation of NF- κ B activity provides a protective effect against the inflammatory state caused by obesity. Polyphenols have also been shown to improve insulin sensitivity and metabolic regulation by modifying the level of acetyl-coA directly. Levels of acetyl-coA strongly determine the activity of acetyl-coA carboxylase which can regulate metabolic flux. Polyphenols also affect the expression of acetyl-coA carboxylase by altering the activity of histone acetyltransferase (HAT) enzymes. These enzymes along with histone deacetylase enzymes (HDAC) appear sensitive to polyphenol interaction and are responsible for epigenetic reprogramming that alter gene expression level. Modifications at the epigenetic level offer re-regulation of metabolism.

A role in cancer prevention and adjuvant therapy also emerges as studies show that epigenetic modifications by polyphenols can limit expression of tumor growth proteins while protecting cells from oxidative damage by traditional therapies. Much of this effect is also due to the limited activity of NF- κ B and activation of Nrf2 that was described previously. Limiting inflammatory proteins while also protecting against oxidative damage reduces the risk of DNA damage that could develop into cancer. In addition to the effects on HATs and HDACs, polyphenols have also been shown to affect DNA methyltransferase (DNMT) activity. These enzymes,

responsible for methylation and demethylation of DNA, are inhibited by polyphenols in general and can limit the methylation level at a gene promoter, thus allowing its expression. One such study showed higher levels of methylation at the BRCA1 gene promoter resulting in decreased expression and shorter interval before disease return. Treatment with catechin polyphenols limited the methylation of BRCA1 and increased disease free intervals. Early studies of adjunctive therapies with polyphenols demonstrate a potential for polyphenols mediated transition metal increased oxidative damage to the cancer cells that can overcome the cancerous cells' increased ability to handle oxidative stress and therefore achieve cell death. There is still much to be studied regarding this pro-oxidant effect of transition metal interaction with polyphenols, but the potential to target cancer cells more directly is encouraging.

A summary of the potential for polyphenols to be used to reduce inflammatory markers, particularly the one associated with a most negative outcome, are suppressed with the addition of certain polyphenols. An overlap exists between the suppression of inflammatory factors and the potential for metabolic re-regulation. In addition to the effects on metabolic regulation achieved by decreasing inflammation, polyphenols also offer improved support of metabolic regulation via metabolic enzyme control and transcription factor mediation. Epigenetic effects cross over between metabolic control and anti-cancer potential, demonstrating again the potential for multi-targeted benefits.

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References

- [1] Brennemna M, Stockert A, Kinder D, Mahfouz T. Docking of select cinnamon components suggest potential for Sirt-1 activation similar to resveratrol. *International Journal Of Pharmaceutical And Phytopharmacological Research*. 2020;10(5):110-121
- [2] Sin TK, Yung BY, Siu PM. Modulation of SIRT1-Foxo1 signaling axis by resveratrol: Implications in skeletal muscle aging and insulin resistance. *Cell Physiol Biochem*. 2015;35(2):541-552. DOI:10.1159/000369718
- [3] Xiong S, Salazar G, Patrushev N, Alexander RW. FoxO1 mediates an autofeedback loop regulating SIRT1 expression. *J Biol Chem*. 2011;286(7):5289-5299. DOI:10.1074/jbc.M110.163667
- [4] Hariharan N, Maejima Y, Nakae J, Paik J, DePinho RA, Sadoshima J. Deacetylation of FoxO by Sirt1 plays an essential role in mediating starvation-induced autophagy in cardiac Myocytes. *Circulation Research*. 2010;107(12):1470-1482. DOI:10.1161/CIRCRESAHA.110.227371
- [5] Cao J, Han J, Xiao H, Qiao J, Han M. Effect of tea polyphenol compounds on anticancer drugs in terms of anti-tumor activity, toxicology, and Pharmacokinetics. *Nutrients*. 2016;8(12). DOI:10.3390/nu8120762
- [6] Cao H, Polansky MM, Anderson RA. Cinnamon extract and polyphenols affect the expression of tristetraprolin, insulin receptor, and glucose transporter 4 in mouse 3T3-L1 adipocytes. *Arch Biochem Biophys*. 2007;459(2):214-222. DOI:10.1016/j.abb.2006.12.034
- [7] Shen Y, Honma N, Kobayashi K, Jia LN, Hosono T, Shindo K, et al. Cinnamon extract enhances glucose uptake in 3T3-L1 adipocytes and C2C12 myocytes by inducing LKB1-AMP-activated protein kinase signaling. *PLoS One*. 2014;9(2):e87894. DOI:10.1371/journal.pone.0087894
- [8] Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget*. 2017;9(6):7204-7218. DOI:10.18632/oncotarget.23208
- [9] Ellulu MS, Patimah I, Khaza'ai H, Rahmat a, abed Y. obesity and inflammation: The linking mechanism and the complications. *Arch Med Sci*. 2017;13(4):851-863. DOI:10.5114/aoms.2016.58928
- [10] Yu JY, Choi WJ, Lee HS, Lee JW. Relationship between inflammatory markers and visceral obesity in obese and overweight Korean adults: An observational study. *Medicine (Baltimore)*. 2019;98(9):e14740. DOI:10.1097/md.00000000000014740
- [11] Poyton RO, Ball KA, Castello PR. Mitochondrial generation of free radicals and hypoxic signaling. *Trends in Endocrinology and Metabolism*. 2009;20(7):332-340. DOI:10.1016/j.tem.2009.04.001
- [12] Hussain SP, Hofseth LJ, Harris CC. Radical causes of cancer. *Nature Reviews Cancer*. 2003;3(4):276-285. DOI:10.1038/nrc1046
- [13] Hussain T, Tan BA-O, Yin Y, Blachier F, Tossou MC, Rahu N. Oxidative Stress and Inflammation: What Polyphenols Can Do for Us? (1942-0994 (Electronic))
- [14] Giampieri F, Alvarez-Suarez JM, Mazzoni L, Forbes-Hernandez TY, Gasparrini M, González-Paramàs AM, et al. An anthocyanin-rich strawberry extract protects against oxidative stress damage and improves mitochondrial functionality in human dermal

- p>fibroblasts exposed to an oxidizing agent.
- Food Funct.*
- 2014;5(8):1939-1948. DOI:10.1039/c4fo00048j
- [15] Cheng Y-C, Sheen J-M, Hu WL, Hung Y-C. Polyphenols and Oxidative stress in atherosclerosis-related ischemic heart disease and stroke. *Oxidative Medicine and Cellular Longevity.* 2017;2017:8526438. DOI:10.1155/2017/8526438
- [16] Ramos S. Cancer chemoprevention and chemotherapy: Dietary polyphenols and signalling pathways. *Molecular nutrition and food research.* 2008;52(5): 507-526
- [17] Jardim BV, Moschetta MG, Leonel C, Gelaleti GB, Regiani VR, Ferreira LC, et al. Glutathione and glutathione peroxidase expression in breast cancer: An immunohistochemical and molecular study. *Oncology reports.* 2013;30(3):1119-1128. DOI:10.3892/or.2013.2540
- [18] Karunaweera N, Raju R, Gyengesi E, Münch G. Plant polyphenols as inhibitors of NF- κ B induced cytokine production—A potential anti-inflammatory treatment for Alzheimer's disease? *Frontiers in Molecular Neuroscience.* 2015;8:24
- [19] Diaz-Ruiz R, Uribe-Carvajal S, Devin A, Rigoulet M. Tumor cell energy metabolism and its common features with yeast metabolism. *Biochim Biophys Acta.* 2009;1796
- [20] Ahmed SM, Luo L, Namani A, Wang XJ, Tang X. Nrf2 signaling pathway: Pivotal roles in inflammation. *Biochim Biophys Acta Mol Basis Dis.* 2017;1863(2):585-597. DOI:10.1016/j.bbadis.2016.11.005
- [21] Ruiz PA, Haller D. Functional diversity of flavonoids in the inhibition of the proinflammatory NF- κ B, IRF, and Akt signaling pathways in murine intestinal epithelial cells. *The Journal of nutrition.* 2006;136(3):664-671
- [22] Zhou Y, Jiang Z, Lu H, Xu Z, Tong R, Shi J, et al. Recent advances of natural Polyphenols activators for Keap1-Nrf2 Signaling pathway. *Chemistry and Biodiversity.* 2019;16(11):e1900400. DOI:10.1002/cbdv.201900400
- [23] Nannini DR, Joyce BT, Zheng Y, Gao T, Liu L, Yoon G, et al. Epigenetic age acceleration and metabolic syndrome in the coronary artery risk development in young adults study. *Clinical Epigenetics.* 2019;11(1):160. DOI:10.1186/s13148-019-0767-1
- [24] van Steenwyk G, Roszkowski M, Manuella F, Franklin TB, Mansuy IM. Transgenerational inheritance of behavioral and metabolic effects of paternal exposure to traumatic stress in early postnatal life: Evidence in the 4th generation. *Environmental Epigenetics.* 2018;4(2). DOI:10.1093/eep/dvy023
- [25] Zhu Z, Cao F, Li X. Epigenetic programming and Fetal metabolic programming. *Frontiers in Endocrinology.* 2019;10:764
- [26] Miska EA, Ferguson-Smith AC. Transgenerational inheritance: Models and mechanisms of non-DNA sequence-based inheritance. *Science.* 2016;354(6308):59-63
- [27] Huypens P, Sass S, Wu M, Dyckhoff D, Tschöp M, Theis F, et al. Epigenetic germline inheritance of diet-induced obesity and insulin resistance. *Nature genetics.* 2016;48(5):497-499
- [28] Houde A-A, Ruchat S-M, Allard C, Baillargeon J-P, St-Pierre J, Perron P, et al. LRP1B, BRD2 and CACNA1D: New candidate genes in fetal metabolic programming of newborns exposed to maternal hyperglycemia. *Epigenomics.* 2015;7(7):1111-1122
- [29] Tzika E, Dreker T, Imhof A. Epigenetics and metabolism in health and disease. *Frontiers in Genetics.* 2018;9:361

- [30] Galdieri L, Vancura A. Acetyl-CoA carboxylase regulates global histone acetylation*♦. *Journal of Biological Chemistry*. 2012;287(28):23865-23876. DOI:10.1074/jbc.M112.380519
- [31] Jo C, Park S, Oh S, Choi J, Kim E-K, Youn H-D, et al. Histone acylation marks respond to metabolic perturbations and enable cellular adaptation. *Experimental & Molecular Medicine*. 2020;52(12):2005-2019. DOI:10.1038/s12276-020-00539-x
- [32] Gothai S, Ganesan P, Park S-Y, Fakurazi S, Choi D-K, Arulselvan P. Natural Phyto-Bioactive Compounds for the Treatment of Type 2 Diabetes: Inflammation as a Target. *Nutrients* [Internet]. 2016 2016/08//; 8(8). Available from: <http://europepmc.org/abstract/MED/27527213>
- [33] Ana GM, Maria LF. The relevance of dietary Polyphenols in cardiovascular protection. *Current Pharmaceutical Design*. 2017;23(17):2444-2452. DOI:10.2174/1381612823666170329144307
- [34] Cheon BS, Kim Yh Fau-Son KS, Son Ks Fau-Chang HW, Chang Hw Fau-Kang SS, Kang Ss Fau-Kim HP, Kim HP. Effects of prenylated flavonoids and biflavonoids on lipopolysaccharide-induced nitric oxide production from the mouse macrophage cell line RAW 264.7 (0032-0943 (Print))
- [35] Villeneuve LM, Natarajan R. The role of epigenetics in the pathology of diabetic complications. *American Journal of Physiology-Renal Physiology*. 2010;299(1):F14-F25. DOI:10.1152/ajprenal.00200.2010
- [36] Mishra A, Sharma A, Kumar S, Saxena A, Pandey A. Bauhinia variegata leaf extracts exhibit considerable antibacterial, antioxidant, and anticancer activities. *BioMed Research International*. 2013;2013
- [37] Anderson RA. Chromium and polyphenols from cinnamon improve insulin sensitivity (0029-6651 (Print))
- [38] Santos HO, da Silva GAR. To what extent does cinnamon administration improve the glycemic and lipid profiles? (2405-4577 (Electronic))
- [39] Hoehn AN, Stockert AL. The Effects of *Cinnamomum cassia* on Blood Glucose Values are Greater than those of Dietary Changes Alone. *Nutrition and Metabolic Insights*. 2012;5:NMI.S10498. DOI:10.4137/NMI.S10498
- [40] Vanschoonbeek K, Thomassen Bj Fau-Senden JM, Senden Jm Fau-Wodzig WKWH, Wodzig Wk Fau-van Loon LJC, van Loon LJ. Cinnamon supplementation does not improve glycemic control in postmenopausal type 2 diabetes patients (0022-3166 (Print))
- [41] Stockert AL, Hill M. Anticancer potential of dietary Polyphenols. In: Waly MI, Rahman MS, editors. *Bioactive Components, Diet and Medical Treatment in Cancer Prevention*. Cham: Springer International Publishing; 2018. p. 25-50. DOI:10.1007/978-3-319-75693-6_2
- [42] Galadari S, Rahman A, Pallichankandy S, Thayyullathil F. Reactive oxygen species and cancer paradox: To promote or to suppress? *Free Radical Biology and Medicine*. 2017;104:144-164. DOI:10.1016/j.freeradbiomed.2017.01.004
- [43] Brglez Mojzer E, Knez Hrnčič M, Škerget M, Knez Ž, Bren U. Polyphenols: Extraction Methods, Antioxidative Action, Bioavailability and Anticarcinogenic Effects. *Molecules* (Basel, Switzerland). 2016;21(7):901. DOI:10.3390/molecules21070901

- [44] Srividhya R, Jyothilakshmi V, Arulmathi K, Senthilkumaran V, Kalaiselvi P. Attenuation of senescence-induced oxidative exacerbations in aged rat brain by (–)-epigallocatechin-3-gallate. *International journal of developmental neuroscience: The official journal of the international society for Developmental Neuroscience*. 2008;26(2):217-223. DOI:10.1016/j.ijdevneu.2007.12.003
- [45] Gill JG, Piskounova E, Morrison SJ. Cancer, oxidative stress, and metastasis. *Cold Spring Harbor Symposia on Quantitative Biology*. 2016;81:163-175
- [46] Ju H-Q, Lin J-F, Tian T, Xie D, Xu R-H. NADPH homeostasis in cancer: Functions, mechanisms and therapeutic implications. *Signal Transduction and Targeted Therapy*. 2020;5(1):231. DOI:10.1038/s41392-020-00326-0
- [47] Ciccarese F, Ciminale V. Escaping Death: Mitochondrial Redox Homeostasis in Cancer Cells (2234-943X (Print))
- [48] Eghbaliferiz S, Iranshahi M. Prooxidant activity of Polyphenols, flavonoids, Anthocyanins and carotenoids: Updated review of mechanisms and Catalyzing metals. *Phytotherapy Research*. 2016;30(9):1379-1391. DOI:10.1002/ptr.5643
- [49] Mileo AM, Miccadei S. Polyphenols as modulator of oxidative stress in Cancer disease: New therapeutic strategies. *Oxid Med Cell Longev*. 2016;2016:6475624. DOI:10.1155/2016/6475624
- [50] Khan HY, Zubair H Fau-Ullah MF, Ullah Mf Fau-Ahmad A, Ahmad A Fau-Hadi SM, Hadi SM. A prooxidant mechanism for the anticancer and chemopreventive properties of plant polyphenols (1873-5592 (Electronic))
- [51] Chen Q, Espey MG, Sun AY, Pooput C, Kirk KL, Krishna MC, et al. Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice. *Proc Natl Acad Sci U S A*. 2008;105(32):11105-11109. DOI:10.1073/pnas.0804226105
- [52] Zheng L-F, Dai F, Zhou B, Yang L, Liu Z-L. Prooxidant activity of hydroxycinnamic acids on DNA damage in the presence of Cu(II) ions: Mechanism and structure-activity relationship. *Food and Chemical Toxicology*. 2008;46(1):149-156. DOI:10.1016/j.fct.2007.07.010
- [53] Dolcet X, Llobet D, Pallares J, Matias-Guiu X. NF-κB in development and progression of human cancer. *Virchows Archiv*. 2005;446(5):475-482. DOI:10.1007/s00428-005-1264-9
- [54] Yahfoufi N, Alsadi N, Jambi M, Matar C. The Immunomodulatory and anti-inflammatory role of Polyphenols. *Nutrients*. 2018;10(11):1618. DOI:10.3390/nu10111618
- [55] Mackenzie GG, Carrasquedo F, Delfino JM, Keen CL, Fraga CG, Oteiza PI. Epicatechin, catechin, and dimeric procyanidins inhibit PMA-induced NF-κB activation at multiple steps in Jurkat T cells. *The FASEB journal*. 2004;18(1):167-169
- [56] Chiang JW, Karlan BY, Baldwin RL. BRCA1 promoter methylation predicts adverse ovarian cancer prognosis. *Gynecologic oncology*. 2006;101(3):403-410
- [57] Fang M, Chen D, Yang CS. Dietary polyphenols may affect DNA methylation. *The Journal of nutrition*. 2007;137(1):223S-228S
- [58] Shukla S, Zaher H, Hartz A, Bauer B, Ware JA, Ambudkar SV. Curcumin inhibits the activity of

ABCG2/BCRP1, a multidrug resistance-linked ABC drug transporter in mice. Pharmaceutical research. 2009;26(2):480-487. DOI:10.1007/s11095-008-9735-8

[59] Yang H, Villani RM, Wang H, Simpson MJ, Roberts MS, Tang M, et al. The role of cellular reactive oxygen species in cancer chemotherapy. J Exp Clin Cancer Res. 2018;37(1):266-266. DOI:10.1186/s13046-018-0909-x