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Medicinal Chemistry of the Epigenetic Diet and Caloric Restriction

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Abstract

The pronounced effects of the epigenetic diet (ED) and caloric restriction (CR) have on epigenetic gene regulation have been documented in many pre-clinical and clinical studies. Understanding epigenetics is of high importance because of the concept that external factors such as nutrition and diet may possess the ability to alter gene expression without modifying the DNA sequence. The ED introduces bioactive medicinal chemistry compounds such as sulforaphane (SFN), curcumin (CCM), epigallocatechin gallate (EGCG) and resveratrol (RSV) that are thought to aid in extending the human lifespan. CR, although similar to ED in the target of longevity, mildly reduces the total daily calorie intake while concurrently providing all beneficial nutrients. Both CR and ED may act as epigenetic modifiers to slow the aging process through histone modification, DNA methylation, and by modulating microRNA expression. CR and ED have been proposed as two important mechanisms that modulate and potentially slow the progression of age-related diseases such as cardiovascular disease (CVD), cancer, obesity, Alzheimer's and osteoporosis to name a few. While many investigators have examined CR and ED as separate entities, this review will primarily focus on both as they relate to age-related diseases, their epigenetic effects and their medicinal chemistry.

Keywords

Age related diseases; caloric restriction; dietary polyphenols; epigenetics and epigenetic diet

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CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

INTRODUCTION

The term epigenetics was coined by Conrad Waddington in 1942 when he merged the two fields of genetics and epigenesis [1]. Epigenetics is generally defined as heritable changes in gene expression that occur without altering the DNA sequence [2]. Epigenetic modifications including DNA methylation, histone acetylation, and RNA interference may occur through external factors and are widely known for their reversibility. Recently, findings from several epigenetics studies have elucidated several pending mechanistic questions, and have become a common thread for other biomedical research fields. Emerging studies suggest that there may be a correlation between epigenetics, caloric restriction (CR) and organismal longevity [3]. In addition, epigenetic changes have recently been adopted as biomarkers for many age-related diseases [4–6]. Epigenetic modifications may also delay the aging process and impact diverse health benefits by activating numerous intracellular pathways. One leading theory suggests that bioactive phytochemicals including 1-isothiocyanato-4-(methylsulfinyl) butane (sulforaphane/SFN), (2R, 3R)-5,7-dihydroxy-2- (3,4,5-trihydroxyphenyl) - 3-4-dihydro-2H-chromen-3-yl, 3,4,5-trihydroxybenzoate (epigallocatechin gallate/EGCG), 3, 4', 5 tihydroxystilbene (resveratrol/RSV), and (1E, 6E)-7-bis- (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene (curcumin/CCM) play significant roles as epigenetic modifiers [7, 8]. Moreover, these compounds show great potential in delaying aging-processes and the onset of accelerated degenerative diseases with regular consumption, which may eliminate one or more diseases with long-term intake [7–9]. The aforementioned theory is more commonly referred to as the "Epigenetic Diet" as it introduces bioactive compounds that aid in delaying the onset of aging and age-associated disease processes [10] (Table 1). While CR and ED have been studied individually, the two are similar due to their utilization of similar dietary compounds. Notably, phytochemicals used in the ED are often extracted from fruits and vegetables consumed on a CR diet.

Of all the external environmental factors, nutrition is thought to be one of the most important because it assists in modifying the expression of genes at the transcriptional level [11]. Elucidation of the importance of epigenetics and its many biological roles, such as modification of gene expression, has brought innovation to various fields including aging [12]. In addition, lower occurrences of a number of diseases have been reported through implementing of the ED, which is believed to silence chromatin (also observed in CR) [13].

To date, CR is considered to be one of the most effective and beneficial means of delaying the progression of aging, since it involves reducing the daily caloric intake, while simultaneously providing all essential nutrients [14]. The benefits of CR were initially observed by McCay and colleagues (1935), when an *in vivo* study conducted on rodents showed that reducing the total amount of calories ultimately prolonged their lifespan [15]. Since then, a number of studies have confirmed McCay's hypothesis regarding CR and have demonstrated the benefits of a CR diet in a variety of animal models, including yeast [16], worms [17], spiders [18], flies [19], fish [20], mice [21], and rats [22], thereby increasing the probability of developing a method to slow the progression of aging.

CALORIC RESTRICTION'S EFFECTS ON AGING

Aging is often defined as cellular senescence, resulting in the inability of a cell to respond to stress and increased homeostatic imbalance. In addition, aging increases the risk of diseases including but not limited to cancer, Alzheimer's disease, cardiovascular disease, hypertension, diabetes and others [23]. It is generally accepted that one's dietary patterns affect disease and health outcomes [24]. According to Buettner *et al*., genes regulate 25% of longevity, whereas 75% is determined by lifestyle factors such as sleep habits, alcohol beverage consumption, stress levels, exercise, and diet. Furthermore, studies have indicated

that vegetarian dietary patterns of the Seventh Day Adventists play a role in extending the life-span of humans, as well as lowering the risk of developing metabolic syndrome, and has been determined to exert beneficial effects on aging [25–27].

While it was once a goal to solely prolong lifespan, it has become increasingly as important to not only extend the lifespan, but to increase the quality of life as well. Since sanitation, vaccines and antibiotics have become readily available, there has been a decline in deaths from age-related diseases, leading to an increased life expectancy of about 30 years [28]. It is suggested that if the trend continues, most children born today are expected to become centenarians. Many studies have accurately elucidated biological aging processes; however, questions remain regarding whether becoming a centenarian is strictly nature or nurture. The increasing average human lifespan over the past century has motivated investigators to focus their efforts on identifying the lifestyle differences for those with average lifespans as compared to centenarians. A vital factor observed between the two is dissimilarities in diets. For instance, the average centenarian diet consists of more plant proteins, whole grains, monounsaturated fats, and low consumption of red meat, sweets and refined grains [29]. A recent study that predicted the one-year mortality rate in elderly hospital patients found that most centenarians were non-obese, had a lower body mass index and were more physically active than the general population [30]. The results were suggestive of CR, due to the adherence to the Mediterranean diet, which consists mostly of high consumption of olive oil, fruits, vegetables, unrefined cereals and fish in combination with a moderate consumption of wine, and low consumption of meat and meat products [30, 31]. Epidemiological studies conducted in Japan found that urban Japanese people consumed more calories and had a higher incidence of cancer than people of rural Okinawa, where CR was observed [32]. Further, Kromphout and colleagues found that the traditional Okinawan diet provides 90% of consumed calories from carbohydrates, albeit, mostly from vegetable and nutritionally dense food consumption [33]. Additionally, compared to more developed countries, Okinawa has 4–5 times the average number of centenarians. Results also show that compared to the United States with a life expectancy of 84.3 and 81.2 years for women and men respectively, Okinawans live to ages 89.1 and 83.5 years for women and men [34].

A number of dietary compounds that mimic the effects of CR provide evidence that nutritional factors may continue to extend cellular longevity. In fact, resveratrol (RSV), a dietary polyphenol found in red wine, grapes, nuts, and dried fruits, is among the beneficial compounds found to delay the aging process. It is suggested that RSV acts as a Sirtuin1 (SIRT1) activator and has received considerable attention for its role in aging [35]. SIRT1 is important in several cellular processes such as cell and gene regulation. According to Howitz and colleagues, when comparing silent information regulator 2 (Sir2) and SIRT2 yeast and human enzyme analogs, with SIRT1, significant enzyme activation leading to an increase in human lifespan was seen [36]. In addition to the SIRT1 mechanism, others have attempted to find compounds that would actively imitate the effects of CR because of its beneficial outcome. It was also discovered that not only is CR beneficial for delaying aging, it may be equally beneficial in many forms of cancer as it has consistently been shown to prevent tumors in a number of models [37]. More importantly, CR has the ability to reverse aberrant gene expression, in addition to delaying many age-related diseases (Fig. 1). Barger *et al*. fed middle age and old mice either an ad libitum (AL or unrestricted calories diet), CR or a diet with low doses of RSV (4.9 mg/day). The results indicated that low doses of RSV prevented gene expression associated with many age-related diseases such as cancer, diabetes, and aging. It was further concluded that low doses of RSV accurately mimics the effects of CR [38].

CALORIC RESTRICTION AND EPIGENETIC DIET COMPOUNDS HAVE ADVANTAGEOUS EFFECTS ON CARDIOVASCULAR-RELATED DISEASES

Cardiovascular disease (CVD) is the leading cause of death in the United States. It is well understood that long-term consumption of unhealthy food, lack of activity, and poor lifestyle choices lead to an increase in body mass and put individuals at a higher risk for CVD [39]. Studies suggest that CR is exceptionally useful in preventing and reversing cardiovascular disease and other related diseases [40]. More recently, childhood obesity has been implicated in countless cardiovascular incidents.

A clinical study on CR conducted by Fontana *et al*. involved 18 individuals who practiced unrestricted American diets and 18 individuals who practiced CR for at least 6 years. Results showed that CR lowered low-density lipoproteins ("bad" cholesterol or LDL), triglycerides and diastolic blood pressure, displaying advantageous protective effects against CVD [41]. Several other clinical studies further confirm these findings, including an investigation conducted using 13 men and 30 women where resting heart rates, mental and physical health, anthropometric variables, and blood pressure of patients were monitored. Subjects were then placed on a restricted diet that consisted of several ED compounds including those found in: fruits, vegetables, whole grains, legumes, nuts and seeds for 21 days. Results concluded that there was a significant decrease in total cholesterol, LDL, systolic blood pressure, and an increase in high-density lipoproteins (HDL) in both men and women, which aid in reducing the risk factors for CVD [42].

Studies involving the effects of long-term CR on the myocardium of mice have been assessed and after 30 months, the hearts from AL fed and CR mice were analyzed, revealing that long-term caloric restricted mice hearts were protected from both post ischemic functional deficit as well as infarction, which led to lowering the risk of CVD [43]. Similarly, CR results in protective effects in healthy non-obese individuals. Experts examined CR with and without exercise in 36 healthy individuals. In addition, researchers examined the triacylglycerol levels and blood pressure levels, which displayed levels of significant gradual decreases within CR patients and significant increases in the AL control group. Therefore, these results suggest that CR with or without exercise positively reduces CVD risks in healthy non-obese patients [44]. Moreover, spontaneously hypertensive rats that were fed an AL diet for five weeks, then reduced to 90% CR for two weeks, and 60% CR for three weeks, ultimately resulted in a significant decrease in systolic and diastolic blood pressure at the end of the ten week period [45]. More recently, in as study conducted by Morimoto *et al*. the dietary phytochemical CCM was shown to prevent heart failure in mice by averting deterioration of systolic function by inducing the myocardial diameter and wall thickness caused by inhibition of HATs, HDACs and p300 activity [46].

CALORIC RESTRICTION AND EPIGENETIC DIET COMPOUNDS ON CANCER

Cancer is the second leading cause of death in the United States [47] and over the past decade, the trend of cancer incidence has increased exponentially. It is well documented that practicing CR may be one of the most prudent way to avoid diseases associated with aging and cancer [48–53]. Rogozina and colleagues tested the effects of CR on mammary tumorigenesis by placing 10 week old female mice in three groups: AL, Intermittent CR (ICR), and Chronic CR (CCR). The AL group was given a diet high in fats and consumed an unrestricted caloric intake. The intermittent group ate ~50% less than the AL diet for three weeks, followed by three weeks of AL, and the chronic CR group were fed ~75% of the AL diet for six weeks. These data portray a dramatic decrease in mammary tumorigenesis as the

incidence rate was 71.0%, 35.4%, and 9.1% for AL, CCR, and ICR mice, respectively. Ultimately, the effects of low carbohydrates and Western diets on mice tumorigenesis indicated that tumor prevalence in mice on a western diet was ~50% by the age of 1 year, while caloric restricted mice depicted no observed tumors [54]. It was also noted that of the two groups, only one mouse on the western diet attained a normal lifespan, while more than half of the caloric restricted mice superseded that [55].

Further studies conducted by Shelton *et al*. tested the effectiveness of CR by placing mice in AL and CR groups and injecting them with malignant glioma cells. After the injection of the tumor cells, the mice were sacrificed and both ipsilateral and contralateral hemispheres were collected to measure the bioluminescence of the tumor cells. These findings indicated that the total percentage of stained cells within the primary tumor as well as the number of blood vessels were significantly lower in the caloric restricted mouse models, demonstrating that CR not only inhibits tumorigenesis but also inhibits tumor metastasis [56]. Considerable evidence has been presented to demonstrate the benefits of CR in monkeys [57–59], dogs [60], and humans [61–63]. Moreover, Colman *et al*. determined the benefits of CR in non-human primates where 50% of AL and 80% of caloric restricted rhesus monkeys survived past the mean life span [64].

Many believe that the aforementioned ED components are analogous to CR and that dietary phytochemicals can be used to prevent cancer. For example sulforaphane (SFN), an isothiocyanate found in cruciferous vegetables such as broccoli, cauliflower, kale, and Brussels sprouts, has been shown to hold great chemopreventive potential [65, 66]. Although SFN has several epigenetic implications, it is most recognized for its ability to inhibit HDACs. Multiple studies have demonstrated the importance of SFN as a chemopreventive agent due to its ability to induce apoptosis, slow tumor growth, and re-express silenced tumor genes [67–69].

An expanding body of preclinical evidence also suggests that the human telomerase reverse transcriptase *(hTERT)* gene may be a viable target for cancer diagnosis, due to its upregulation (90%) in cancer cells in comparison to somatic cells. *hTERT* is regulated by epigenetic modifications at promoter sites such as histone acetylation, histone methylation, and DNA methylation [70, 71]. Histone acetyltransferases (HATs) are enzymes that allow acetyl groups to be transferred to lysine residues in histones, while histone deacetylases (HDACs) remove acetyl groups in order to promote an open chromatin structure. This in turn facilitates the repression or expression of critical genes such as *MAD1*, *CTCF*, and *hTERT*. The *hTERT* promoter region is hyper-methylated by DNA methyltransferases (DNMTs), namely DNMT1 (which is responsible for maintaining methylation). The demethylation of CpG islands encourages CTCF binding on the *hTERT* promoter, thereby repressing *hTERT*. This may offer novel insights on possible targets in human cancer cell lines [72] (Fig. 1). In addition, investigators have found that the aberrant hypermethylation of the *hTERT* 5’ regulatory region inhibits the binding of the CTCF repressor to *hTERT* [73]. To further confirm this, Meeran *et al*. treated MCF-7 and MDA-MB-231 breast cancer cells with low doses of the dietary compound SFN, which significantly inhibited expression of human telomerase reverse transcriptase (*hTERT)*, decreased DNA methyltransferases levels (*DNMT1 and DNMT3*a), and initiated the process of cellular apoptosis in both breast cancer cell lines. It was also found that SFN allowed transcriptional repressors to bind to the *hTERT* 5’ regulatory region, thereby decreasing the viability and proliferation of the cancer cells [74] (Table 2).

The green tea polyphenol, EGCG, is believed to inhibit cancer through several epigenetic modifications. EGCG is widely consumed in many countries and has become a delaying agent for many diseases. Although the mechanism through which EGCG acts is not

thoroughly understood, numerous studies have suggested that hypermethylation of CpG islands is a vital mechanism that silences the expression of an abundance of cancer-related genes. Nandakumar *et al*. tested the effects of EGCG on A431 (skin) and SCC (squamous) cell carcinoma lines and found that EGCG decreased levels of epigenetic modifiers 5-methylcytosine, methylated H3-Lys 9, DNMT1, DNMT3a, DNMT3b, and HDACs, while increasing levels of acetylated lysine 9 and 14 on histone H3 (H3- Lys 9 and 14) and acetylated lysine 5, 12, and 16 on histone H4. Additionally, EGCG treatments caused a re-expression of the mRNA and proteins of silenced *p16ink4a* and *Cip1/p21* genes [75]. Fang and colleagues further confirmed this mechanism when they performed a similar experiment on KYSE 510 and 150 (human esophageal squamous cell sarcoma) cell lines, which produced similar results [76]. Berletch and others also showed the relationship of EGCG and epigenetics, when MCF-7 (breast) and HL 60 (leukocyte) cells treated with EGCG were shown to down-regulate *hTERT*, due to paradoxical decreases in the methylation of the *hTERT* promoter [77].

Studies conducted by Papoutsis *et al*. treated MCF-7 (breast) cancer cells with RSV to combat the effects of aromatic hydrocarbon receptors (AHR), synonymous for contributing to the etiology of numerous types of malignancies. The authors investigated the effects of AHR with agonist 2,3,7,8 tetrachlorobenzo (p) dioxin (TCDD) on the BRCA-1 gene, which revealed that activation of AHR to the BRCA-1 gene promoter hampers 17βestradiol-dependent stimulation on protein and transcriptional levels. In addition, the treatment of TCDD increased mono-methylated Histone 3 Lysine 9 (H3K9) and DNA methyltransferase 1 (DNMT1), and stimulated the accumulation of DNA strand breaks. It was determined that RSV actively reversed detrimental effects of AHR agonists via epigenetic modifications and in turn the silenced BRCA-1 gene was expressed [78].

CALORIC RESTRICTION AND EPIGENETIC DIET COMPOUNDS MAY AFFECT OBESITY AND INFLAMMATION

Obesity accounts for nearly 300,000 deaths per year in the United States alone [79]. Recent reviews have addressed the need to understand and combat the obesity epidemic and energy balance CR. An increase in energy dense foods and lack of activity appear to be among the leading causes of obesity and related diseases [80]. It has also been suggested that obesity is associated with an immunodeficiency state and chronic inflammation, and that CR and obesity are reciprocal mechanisms capable of regulating immunity and health span, making it a possible target for delaying the aging process [81].

A recent study tested the effects of CR on pulmonary functions and determined markers for oxidative stress, inflammation, and quality of life in caloric restricted overweight asthma patients. In this study, ten patients with a body mass index greater than 30 were maintained for eight weeks, while alternating every other day between an AL and caloric restricted diet (20% less than AL). Questionnaires and blood samples were collected for markers of general health, oxidative stress, and inflammation. Within two weeks of initiation of the diet, the quality of life and levels of antioxidant uric acid increased significantly. Furthermore, inflammation serum tumor necrosis factor-α (TNFα) and brain derived neurotropic factor was decreased. More recently, the effects of CR, weight loss, and exercise on inflammatory biomarkers were examined in nearly 500 obese women. Inflammatory marker- high sensitivity C-reactive protein (hs-CRP), serum amyloid A (SAA), and interleukin-6 (IL-6), leukocyte, and neutrophil levels were measured. The levels in all markers decreased significantly and it was concluded that CR with and without exercise decreases biomarkers of inflammation in overweight asthma patients [82]. To further address this, Schulte *et al*. monitored 23 obese individuals (BMI 44.1 ± 1.1 kg/m^2) and 12 lean individuals (BMI 22.3 ± 0.4 kg/m^2) who were treated with an 800 kcal/day for 12 weeks. Principal findings

concluded that pro-inflammatory protein genes, *wnt5a* and *sFRP5*, were not measurable in serum in lean individuals but were consistently detectable in obese subjects. Concluding that CR constructively affects serum concentrations in obese individuals [83].

More recently, pre-clinical studies performed by Nagao *et al*. showed the anti-obesity effects of RSV by feeding rats an Otsuka Long-Evans Tokushima fatty (OLETF) diet supplemented with RSV. While OLETF rats suffer from hyperplasia, causing them to become obese with even a normal diet, the results indicated that their fat metabolism significantly decreased in four short weeks due to the adherence of the ED compound [84]. To further confirm these findings, Weisberg and colleagues performed a similar experiment on *ob/ob* male C57BL/6J mice, where their diet was supplemented with CCM. Their results showed that the addition of CCM in the diets caused a significant decrease in white adipose tissue, hepatomegaly, hepatic nuclear factor-κB activity and markers of hepatic inflammation, while simultaneously increasing adipose tissue adiponectin production. Thereby, ultimately reversing many symptoms commonly associated with obesity [85].

CALORIC RESTRICTION AND EPIGENETIC DIET COMPOUNDS MAY BE EFFECTIVE AGAINST NEURODEGENERATIVE DISEASES

An estimated 5.4 million Americans are currently living with Alzheimer's disease (AZD). It was originally believed that AZD was the only disease in the top ten causes of death that could not be prevented, cured, or delayed. However, recent discoveries have refuted these beliefs. In a clinical trial fifty elderly normal and overweight individuals were split into three groups: 1) CR 2) relative increase of unsaturated fatty acids and 3) control. Memory was tested before and after intervention and findings supported higher synaptic plasticity and stimulation of neuroprotective pathways in the brain, which resulted in a significant increase in memory scores in the caloric restricted patients but no change in the control or relative increase of unsaturated fatty acid groups [86].

Epidemiological and *in vivo* studies suggest that tea consumption and neurodegenerative diseases such as dementia, AZD, and Parkinson's disease (PD) have inverse relationships [87]. Several clinical studies found that two or more cups of green tea (EGCG) per day significantly reduces the risk of PD and results in a lower occurrence of cognitive impairment [88–90]. Additional studies found that several vitamins further support the inverse relationship between bioactive compounds and neurodegenerative diseases. Clinical trials conducted by Wengreen *et al*. followed 3831 residents who were above the age of 65 for seven years. Each patient was given a questionnaire and cognitive function assessment by following the modified mini mental state examination. Investigators found that high consumption of vitamins A, E, C, and carotene slowed the progression of AZD in elderly patients [91].

Experimental studies suggest that the epigenetic modifying polyphenol curcumin (CCM), found in the Indian spice turmeric, is a beneficial compound in slowing the progression of AZD. Xiong and colleagues treated SH-SY5Y (neuroblastoma) cells with CCM at 0, 1.25, 5.0, and 20 μM for 24, or 5.0μM for 0, 12, 24, and 48 h. The results indicated that CCM decreases the Amyloid Beta (Aβ) (a peptide most commonly associated with AZD) production by inhibiting glycogen synthase kinase 3 beta (GSK-3β) mediated Presenilin 1 (PS1) activation, lowering the occurrence of AZD [92]. These results have been observed both *in vivo* [93] and *in vitro* studies, [94] (Table 2). Moreover, epidemiological studies conducted in India where CCM is highly consumed and AZD affects a small percentage of the population, have confirmed these findings [95].

CALORIC RESTRICTION MAY REDUCE BONE DISEASES

Osteoporosis occurs as a result of diminishing bone tissue and decreases in bone density over time. It is a common disease affecting the elderly (mostly women) [96]. Recently, *in vitro* and *in vivo* experiments have highlighted the importance of nutrition in gene studies [97]. An *in vivo* study conducted by Zhang and colleagues fed rats an AIN 93G diet (designed for expecting rodents for growth requirements) with or without blueberries before the onset of puberty, post-natal day 20, and postnatal day 34. Results suggest that early exposure to blueberries inhibited ovariectomy in adult rats by increasing myosin levels that are generally known to be decreased with the disease. It was suggested that the anti-antagonist relationship between blueberries and myosin inhibit osteoblasts from entering senescence by regulating the *Runx2* gene and balancing myosin levels [98].

The controversial topic of CR and arthritis has received attention over the past few years due to the misinterpretation of the definition of CR. Although CR is defined as the process of consuming fewer calories without malnutrition, it is often assumed that losing weight is suggestive of lowering disease incidence. Numerous studies evaluate the inverse relationship between osteoarthritis and body mass index in association with dietary restriction [99–101]. Messier *et al*. tested the effects of intensive dietary restriction with or without exercise or only exercise on 450 patients with osteoarthritis (OA) in one or both knees, with no history of minimal activity (30 min. or less) in the past six months. Results revealed that although there was a decrease in body mass index in patients who practiced exercise only, weight loss unaccompanied by dietary restriction was not suggestive of slowing the progression of OA. However, intensive dietary restriction induced weight loss intervention and showed beneficial data towards the theory of CR [102]. Marshall *et al*. observed the benefits of weight lost due to CR when they placed 16 canines with OA symptoms, and a body weight of at least 20% above normal, on a CR diet for 18 weeks. The results indicated that the dogs that lost 6.10–8.85% body weight showed vivid improvement in walking and movement [103].

CONCLUSION

In this review, we have discussed the ED and CR and how they affect diseases such as cancer, cardiovascular disease, hypertension, obesity, Parkinson's disease, Alzheimer's disease and osteoporosis. Dietary phytochemicals including: SFN, EGCG, vitamins, CCM, and RSV have been indicated in causing epigenetic modifications upon use, thereby, suggesting that they may be useful as ED compounds and capable of influencing disease processes. Results conducted by studies herein suggest that consumption of bioactive compounds might aid in altering the expression of epigenetic modifying genes such as *DNMTs* and *HDACs*, in addition to disease-related genes such as *hTERT* and *p16*. The epigenetic diet offers some information on gene modifications; however, further investigations are needed in order to determine whether these compounds are effective in altering disease states.

Mounting evidence is suggestive of the benefits of CR in delaying the progression of age-related diseases. Although CR has often been misconstrued as starving oneself to directly target aging, whether CR is detrimental or advantageous in extending human lifespan is still a controversial issue. Perhaps the most beneficial way to target various diseases is to debunk the theory of decreasing one's weight without the addition of bioactive compounds discussed in this review. While there is insufficient data to conclusively determine that there may be an association between the ED and CR, we believe based on data herein, that there is a direct correlation between the two. However, much work is still needed to determine the epigenetic benefits of utilizing bioactive dietary compounds in combination with CR.

In short, the growing field of epigenetics warrants more exploration of the potential of the ED in inhibiting disease progression, as it remains cutting edge and is not thoroughly understood. This may offer a plausible explanation for the scarcity of recent scientific publications on the ED in association with deleterious diseases. This review will undoubtedly spark new topics of exploration involving epigenetic modifying compounds and their potential to reverse the effects of aging and age-related diseases. This also offers new ideas for future experiments to test the synergistic effects of the two, which may generate novel treatments mimicking the effects of the ED and CR.

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ABBREVIATIONS

AHR	Aromatic hydrocarbon receptors
AL	Ad libitum
AZD	Alzheimer’s disease
Aβ	Amyloid beta
BRCA-1	Breast cancer 1
CR	Caloric restriction
CVD	Cardio vascular disease
CCR	Chronic Caloric Restriction
CCM	Curcumin
CTCF	11-zinc finger protein or CCCTC-binding factor
DNMT 1	DNA methyltransferase 1
DNMT 3a	DNA methyltransferase 3a
DNMT 3b	DNA methyltransferase 3b
EGCG	Epigallocatechin
ED	Epigenetic Diet
GSK 3 β	Glycogen synthase kinase 3 beta
H3K9	Histone 3 Lysine 9
HAT	Histone acetyl transferase
HDL	High density proteins
HS-CRP	High sensitivity c-reactive protein (hs-CRP)
HDAC	Histone deactetylase
HTERT	Human telomerase reverse transcriptase
ICR	Intermittent caloric restriction

IL-6	Interleukin-6
LDL	Low density lipoproteins
MAD-1	Mitotic spindle checkpoint protein
NF-κB	Nuclear Factor kappa B
OA	Osteoarthritis
OLETF	Otsuka Long Evans Tokushima Fatty
PD	Parkinson's disease
PS1	Presenilin 1
ROS	Reactive Oxygen Species
RSV	Resveratrol
Runx 2	Runt-related transcription factor 2
SAA	Serum amyloid A
SAM	S-adenosyl-L-methionine
SAH	S-adenosyl-L-homocysteine
SFN	Sulforaphane
SFRP5	Secreted frizzled-related protein 5
SIR 2	Silent information regulator 2
SIRT 1	Sirtuin 1
SIRT 2	Sirtuin 2
TCDD	2,3,7,8 Tetrachlorobenzo (p) dioxin
TNF α	Tumor necrosis factor

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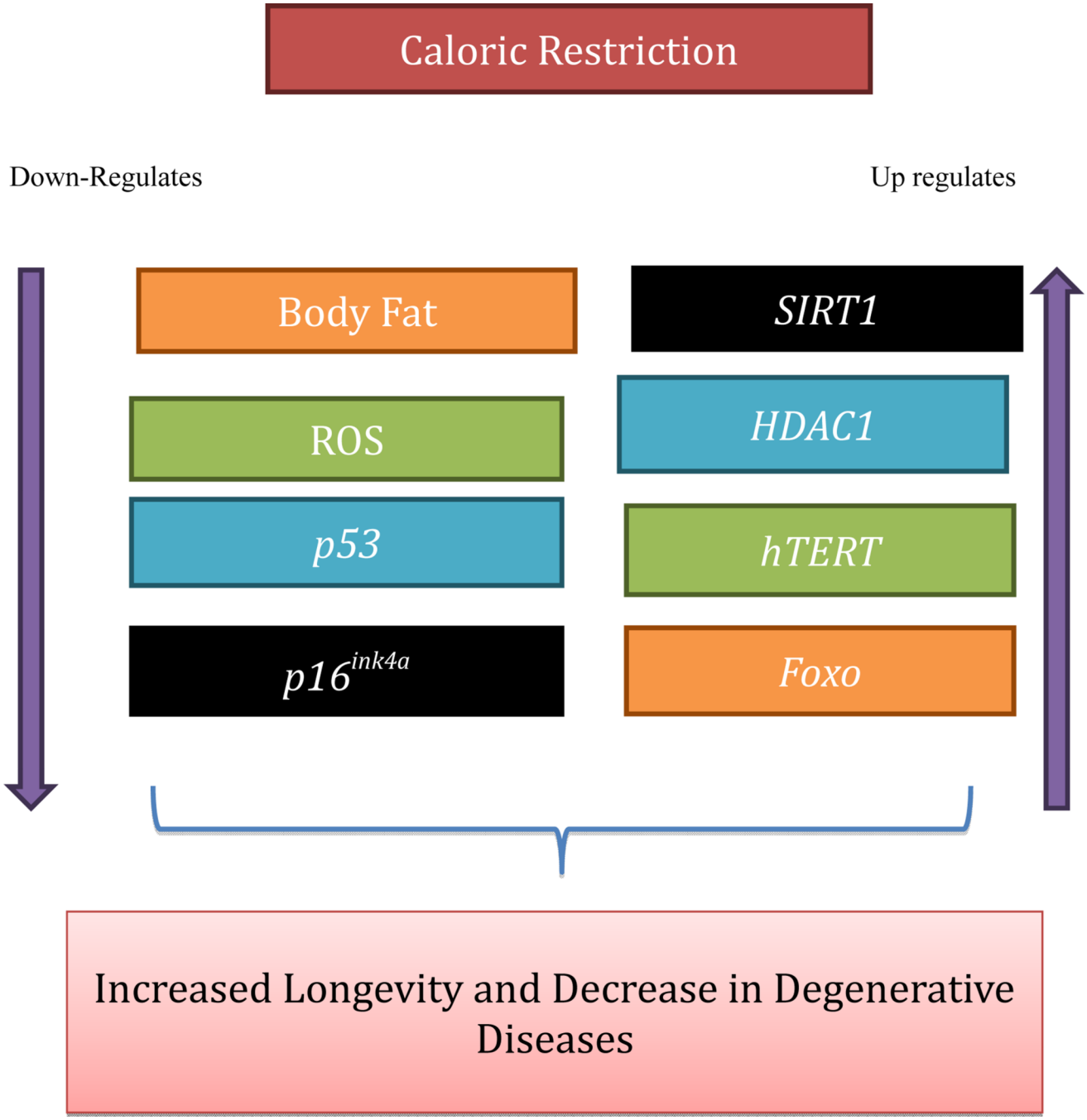


Fig. (1).
The path to longevity. CR displays the upregulation (indicated by upward arrow) and down-regulation (indicated by downward arrow) of vital intracellular pathways that lead to an increased lifespan (indicated by brace).

Table 1

Dietary Phytochemicals, Components of the Epigenetic Diet and Abbreviated Health Effects

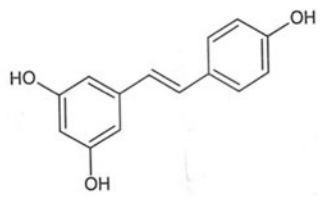
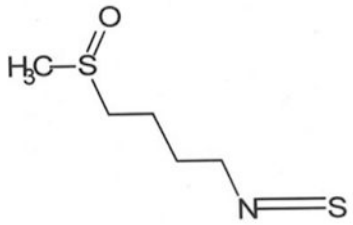
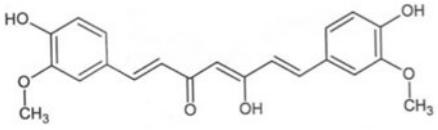
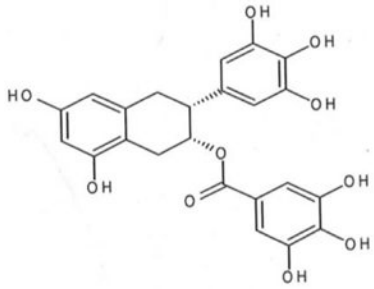
Food	Compound	Structure	Conditions Affected	References
Nuts, grapes, dried fruits	Resveratrol (RSV)		Aging and cancer	[16–18, 20, 21, 38–40]
Brussels sprouts, broccoli, and kale	Sulforaphane (SFN)		Aging and cancer	[61–64, 67–70]
Turmeric	Curcumin (CCM)		Aging and Alzheimer's disease	[76–78, 85–88]
Green tea	Epigallocatechin (EGCG)		Aging and cancer	[7, 12, 28, 71, 72]

Table 2

Epigenetic Diet Compounds and Modifications

Resveratrol (RSV)	Sulforaphane (SFN)	Curcumin (CCM)	Epigallocatechin Gallate (EGCG)
RSV Down-regulates NF-κB causing cell cycle arrest and apoptosis [104]	SFN Down-regulates hTERT inhibiting telomerase activity [74]	CCM Inhibits HDAC activity [105]and HAT activity [46]	EGCG Inhibits DNMTs [76]
RSV Up regulates p53 inducing apoptosis [106]	SFN Induces apoptosis [65, 69]	CCM Inhibits Amyloid beta [93, 94]	EGCG Down-regulates hTERT inhibiting telomerase activity [77]
RSV Inhibits HDAC activity [105]	SFN Modulates cyclin D2 [107]	CCM Induce reactive oxygen species (ROS) [108]	EGCG Re-expresses p16 ink4a [109]
RSV Up regulates SIRT1 [17, 110]	SFN Induces phase 2 enzymes [65]	CCM Inhibits DNMTs [111]	EGCG Inhibits HDAC activity [105]
RSV Down-regulates hTERT inhibiting telomerase activity [112]	SFN Inhibits HDAC activity [68]	CCM Inhibits pro-inflammatory cytokines [113]	EGCG Increases p53 transcriptional activity [114]