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REVIEW

Traditional Chinese Medicine

The effects of nutritional ketosis induced by Bigu-herbs regimen and ketogenic diet on diseases and aging

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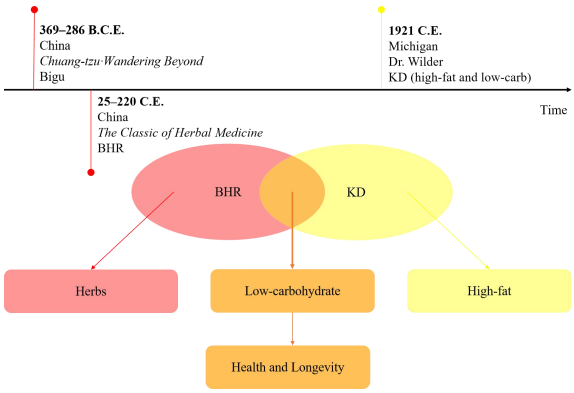
Highlights

Traditional Bigu-herbs regimen (BHR), a Taoism (Taoism is an ancient Chinese Taoist philosophy system) special health-preserving technique to achieve longevity through strict abstinence from food) and modern ketogenic diet can promote the formation of ketone bodies and achieve the state of nutritional ketosis by limiting carbohydrate intake. This review summarizes how ketone bodies or nutritional ketosis affects diseases and the aging process, as well as the side effects of ketogenic diet.

Traditionality

BHR refers to taking herbs with the purpose of reducing appetite and controlling diet and then replacing normal diet. The earliest record of Bigu comes from Zhuangzi·Xiaoyaoyou (*Chuang-tzu·Wandering Beyond*), which was written by Chuang-tzu, a major representative of the Taoist School (369–286 B.C.E.). In the Eastern Han dynasty (25–220 C.E.), the ancient classical medicine monograph, Shennong Bencao Jing (*The Classic of Herbal Medicine*), initiated the practice of BHR for health, which recorded several herbs with weight-loss and life-prolonging properties. Nowadays, there are several preclinical studies and clinical trials of BHR in China, and the results show that BHR has a beneficial clinical effect in the prevention and treatment of metabolic syndrome, autoimmune-related diseases, etc.



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Abstract

The Bigu-herbs regimen, a Taoism (Taoism is an ancient Chinese Taoist philosophy system) special health-preserving technique to achieve longevity through strict abstinence from food, limits the intake of grains and uses herbs to replace normal diet to gain energy. Practicing Bigu-herbs regimen for several weeks to several years can make one lose weight, prevent diseases, and prolong life. The modern ketogenic diet (KD) mainly limits carbohydrate intake and increase fat intake. The low-carbohydrate, high-fat, and adequate protein diet is well known for its antiepileptic and neurotrophic effects. Limiting the intake of carbohydrate results in energy metabolism reprogramming to mobilize the steatolysis, energize and promote ketone bodies (KBs) production, achieving a state of nutritional ketosis (NK). The researchers summarized how ketone bodies or NK affects diseases and the aging process, as well as the side effects of KD. NK has a favorable effect on caloric intake, lipid parameters, glycemic index, and insulin sensitivity; moreover, it can be used as a treatment option for diabetes, obesity, and other metabolic disorders. NK is recognized as being neuroprotective and is good for epilepsy, Alzheimer's disease, and emotional disturbance. Targeting the metabolic differences between tumor and normal cells, NK limits the use of glucose and impairs energy metabolism in cancer cells, inhibiting their growth and rendering them susceptible to clinical treatments. NK also affects inflammation and the release of cytokines, regulate gut flora, extend longevity and health span, and preserve physiologic functions. The side effects of KDs are controllable under the guidance of a specially trained dietitian and medical team.

Keywords: Grain avoidance, Bigu-herbs regimen, Ketogenic diet, Nutritional ketosis, Ketone body

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***Abbreviations*:**

BHR, Bigu-herbs regimen; KD, ketogenic diet; NK, nutritional ketosis; KBs, ketone bodies; IF, intermittent fasting; TGs, triglycerides; β-HB, β-hydroxybutyrate; NAD+, nicotinamide adenine dinucleotide; SGLT2i, sodium-glucose co-transporter-2 inhibitor; AD, Alzheimer's disease; MAD, modified Atkins diet; GABA, gamma aminobutyric acid; RCT, randomized controlled trial; MS, multiple sclerosis.

***Competing interests*:**

There are no conflicts of interest.

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Background

Good health has always been the aspiration of human beings, and keeping one's self fit by adjusting the diet has a long history. Bigu is regarded as a Taoist (Taoism is a Chinese traditional philosophical system developed by of Lao-tzu and Chuang-tzu) special health-preserving technique developed in the context of ancient Chinese Taoist philosophy to achieve longevity through strict abstinence from food, which literally means "grain avoidance", making it similar to fasting [1–4]. Bigu-herbs regimen (BHR) refers to taking herbs with the purpose of reducing appetite and controlling diet and then replacing normal diet [5]. The earliest record of Bigu comes from Zhungzi·Xiaoyaoyou (*Chuang-tzu·Wandering Beyond*), which was written by Chuang-tzu, a major representative of the Taoist School (369–286 B.C.E.) [3]. In the Eastern Han dynasty (25–220 C.E.), the ancient classical medicine monograph, Shennong Bencao Jing (*The Classic of Herbal Medicine*), initiated the practice of BHR for health, which recorded several herbs with weight-loss and life-prolonging properties [6]. Later, Qianjin Yifang (*Supplemental Prescriptions Worth a Thousand in Gold*) and Bencao Gangmu (*Compendium of Materia Medica*) recorded formulae and a large number of prescriptions of BHR [5, 7]. The time of BHR ranges from several weeks to several years. In adapting BHR, an individual reduces the intake of cereals and meat, cuts off food supplementation to less than the minimum required to maintain normal activities, lives on herbs for nourishment and energy, and keeps body in a state of approaching fasting [8–10]. It can enhance immunity, promote weight-loss, benefit nerve activity, prolong life, and comprehensively improve health [5, 6]. Nowadays, there are several preclinical studies and clinical trials of BHR in China, and the results show that BHR has a beneficial clinical effect in the prevention and treatment of metabolic syndrome, autoimmune-related diseases, etc [11–16].

Fasting has a role in adaptive cellular responses that reduce oxidative damage and inflammation, optimize energy metabolism, and strengthen cellular protection. It has the potential to delay aging and help improve disease conditions while minimizing the side effects caused by chronic dietary interventions [17]. Modern medicine has found that physiologic responses to fasting include increased insulin sensitivity and cellular stress resistance, reduced resting blood pressure and heart rate, and increased parasympathetic tone [17]. Fasting also leads to a rise in concentration of ketone bodies (KBs), which are metabolites of fat, with a role in providing energy and sending signals [18–20]. There is a metabolic reprogramming in the body when a person undergoes fasting. The body uses the energy supplied by KBs instead of the energy supplied by glucose [21, 22]. This dietary accumulation of KBs in the blood is known as nutritional ketosis (NK) [23, 24].

In order to keep the body in a state of approaching fasting and ensure necessary nutrition, there is a modern ketogenic diet (KD) reported in Michigan [25, 26]. It is a low-carbohydrate diet that can significantly alter the energy matrix of the body, especially in the brain. KD is known to have an effective anticonvulsant effect [27]. Preliminary evidence has been obtained for its anti-tumor effects and positive influence in regulating immunity, metabolism, nervous system functions, etc [28]. Considering that it is a high-fat diet and the total calories can ensure the basic life requirements, clinical application is being constantly explored [29]. With the people's increasing awareness of health and wellness, KD begins to popularize among the people and received good feedback [30, 31].

Traditional BHR and modern KD may reach a long-term stable NK by limiting carbohydrate intake and adjusting food structure [12, 32]. Here, the researchers reviewed studies in animals and humans that have shown how NK affects metabolism, nervous system functions, tumors, immune system health, lifespan, chronic disease management outcomes, and the aging processes.

Bigu-herbs regimen

BHR is a kind of Taoist regimen similar to fasting. Bigu herbs refer to several plant-based foods or recipes with the homology of medicine, which can prevent diseases and promote health, especially when appetite is reduced and fasting is easier. By taking herbs instead of normal food, BHR reduces or even avoids the intake of carbohydrates and proteins, ranging from several weeks to several years, to keep achieving NK in the body and eventually regulate metabolism, boost immunity, aid nervous system functions, prolong life, promote weight loss, and improve chronic disease management [5, 10, 33, 34].

BHR has a good reputation for thousands of years in China, and its safety and feasibility has been verified, which is beneficial to the problems of hunger because of its compliance and safety in simple fasting therapy [5, 10]. The earliest extant work of Bigu is a silk scroll unearthed from the Mawangdui archaeological site (Han dynasty, 202 B.C.E.–220 C.E.) called Quegu Shiqi (*Grain Avoidance and Eating Qi*) in Changsha, China. The silk manuscripts were written around the periods of Gao and Hui emperors (206–188 B.C.E.) [3]. The famous historiographer Si Maqian (91 B.C.E.) recorded Bigu as a treatment for disease in Shiji (*Records of the Grand Historian*), which is China's first general chronicle [5, 35].

In the Eastern Han dynasty (25–220 C.E.), Shennong Bencao Jing (*The Classic of Herbal Medicine*) officially recorded the BHR and the 18

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herbs that were used [10]. Sun Simiao (541–682 C.E.), a famous physician in the Tang dynasty (618–907 C.E.), emphasized the medical effects about BHR in his medical book Qianjin Yifang (*Supplemental Prescriptions Worth a Thousand in Gold*) [7]. Subsequently, the medical book Bencao Gangmu (*Compendium of Materia Medica*) that was written by Li Shizhen (1518–1593 C.E.), a famous physician and pharmacologist in the Ming Dynasty (1368–1644 C.E.), and other books recorded numerous transcriptions of BHR [10, 34]. The main herbs were Baizhu (*Atractylodis Macrocephalae Rhizoma*), Huangqi (*Astragali Radix*), Huangjing (*Rhizoma Polygonati*), Fupenzi (*Rubi Fructus*), Dazao (*Jujubae Fructus*), Yiyiren (*Coicis Semen*), Gancao (*Glycyrrhizae Radix et Rhizoma*), Renshen (*Ginseng Radix et Rhizoma*), Cangzhu (*Atractylodis Rhizoma*), Shihu (*Dendrobii Caulis*), Yuanzhi (*Polygalae radix*), Niuxi (*Achyranthis bidentatae Radix*), and Wuweizi (*Schisandrae Chinensis Fructus*) [5, 7, 36]. These herbs were described as rich in lipids and protein, sufficient the basic needs of the body, time-taking to digest and metabolize, and energy-boosting [5, 33]. On the basis of replenishing energy and improving health, adding herbs may help remove impurities and prolong life (such as Shiwei (*Folium Pyrrosiae*)) [5]. At present, a number of individuals in China and other parts of the world continue to practice BHR for weight loss, health, and longevity. Clinical trials are also gradually confirming the role of this ancient traditional regimen [3, 5, 37].

KD and fasting

What is KD? It is a high-fat, low-carbohydrate, and adequate protein diet which limits glucose availability and causes a metabolic reprogramming of the body's energy source because KBs replace glucose for energy [38]. KD originated in the treatment of epilepsy by fasting. In 1921, children with intractable epilepsy fasted for 3 weeks under the guidance of a Michigan pediatrician named Dr. Hugh Conklin and a certain faith healer [25].

Fasting can be divided into three types: caloric restriction, dietary restriction, and intermittent fasting (IF) [39]. IF is currently having more research and gradually gaining popularity among folks, and its methods include: (1) limiting time consumption, which means limiting your intake to 6–8 hours [40]; (2) "5: 2 IF" which means eating only a moderate amount of food 2 out of 7 days a week [17]; (3) alternate-day fasting, which is fasting and eating over a 24h period, respectively. The point is not to obsessively limit total calorie intake but to alter the frequency of food consumption [41]. IF elicits evolutionarily conserved, adaptive cellular responses that improves glucose regulation, suppresses inflammation, and increases stress resistance. During fasting, cells activate pathways that enhance intrinsic defenses and remove or repair damaged molecules. After resumption of feeding, cells engage in tissue-specific processes of growth and plasticity [42].

The KD mimics a metabolic state of fasting, inducing a metabolic reprogramming toward mobilizing the steatolysis to energize the body. One of the common metabolic changes assumed to take place when a person follows fasting is ketosis [43]. To imitate this state of ketosis caused by fasting, Dr. Wilder first described this high-fat and low-carbohydrate diet in the same year [26]. It is essentially the same KD that is in use now [27]. The carbohydrate restriction of the KD keeps glucose and insulin levels low and stable, activating gluconeogenesis and forcing fatty-acid conversion to ketogenesis.

As the KD approaches 100 years of continuous use, it is becoming ever more mature, and the effect is gradually demonstrated. There are four types of KDs [45], namely classic ketogenic diet, modified Atkins diet (MAD), medium-chain triglyceride diet, and low glycemic index treatment. The researchers also compared the KDs to the standardized American diet and Chinese residents' diet (Table 1). In general, The KDs provides nutrition with 1g/kg protein and net carbohydrates (excluding dietary fiber and other non-absorbable substances) ≤ 50 g or < 5% of energy intake per day, with the remainder of calories as fat [44, 45]. The ratio of fat to carbohydrate and protein ranges from 2:1 to 4:1, with higher ratios seen as probably more effective [46]. The MAD is 70% fat and 5% carbohydrate and could achieve NK if carbohydrates are reduced sufficiently. In this case, MAD will have better compliance for similar benefits in disease control with a less restrictive diet [47, 48]. Comparing the efficiency of different fats in inducing ketosis, an animal study demonstrated the rank order of induced NK was medium-chain triglycerides > flaxseed oil

Table 1 Energy supply ratio of three major nutrients in ketogenic diet

	Carbohydrate (calories %)	Fat (calories %)	Protein (calories %)
CKD	3	90	7
MAD	5	70	25
MCTD	20	70	10
LGIT	27	45	28
SAD	50	35	15
CRD [49]	55–65	20–30	10–15

CKD, classic ketogenic diet; MAD, modified Atkins diet; MCTD, medium-chain triglyceride diet; LGIT, low glycemic index treatment; SAD, standardized American diet; CRD, Chinese residents' diet.

≥ lard = butter [50]. With the increase of the people's health awareness and attention to NK, the number of clinical research increases around the 21st century [27]. Some KD preparations have also been put into research and application [51]. It is possible to elevate blood ketones artificially with KB supplementation or ketogenic agents, which could cause a more sustained production of KBs [52]. Animal researches suggest that an exogenous ketone-supplemented KD makes it easier to maintain NK and offer a more efficacious therapy than KD alone [53].

KDs provide the KBs that are necessary to fuel cells, cause energy metabolic reprogramming, reach a state of NK, and elicit highly orchestrated systemic responses to bolster mental and physical performance, as well as disease resistance.

Metabolic reprogramming and nutritional ketosis

Glucose and fats are the body's major sources of energy. After meals, glucose is used for energy, and fat is kept in adipose tissue as triglycerides (TGs). The inadequate availability of carbohydrates in BHR or KD, mimicking that of fasting, triggers metabolic reprogramming, an ancient adaptation to times of food scarcity. Cells deplete the faster sugar-based energy reserves and begin to convert fat into energy in a slower metabolic process. In humans, fasting for 12–24 h generally results in glucose depletion and liver glycogen loss of ≥ 20% and triggers a series of negative feedback regulatory mechanisms, including increased glucagon secretion, increased production of endogenous glucose, improved insulin sensitivity, and maintained increase in allogeneic glucose levels [17, 54]. In this metabolic condition, the body burns fats rather than carbohydrates to provide energy. TGs in adipose tissue are hydrolyzed into fatty acids that are released into hepatic cells through the bloodstream to produce KBs, providing a major source of energy for the body and brain, which is delivered by crossing the blood-brain barrier. KBs also diminish glutamine uptake, decrease the level of c-Myc, a metabolic master regulator, and recruit glycolytic gene promoters [55–58].

There are three KBs known, namely (1) acetoacetate, the central KB in energy metabolism; (2) β-hydroxybutyrate (β-HB), the primary circulating KB; (3) acetone [18, 59]. Low-carbohydrate intake also results in a reduction of the circulating insulin level, which promotes a high level of circulating fatty acids [19]. Human nutrition begins with KB. Colostrum is ketogenic and serves the needs of the neonate completely [60]. The muscles, especially the heart, can easily utilize KBs while the brain utilizes KBs only in long-term NK. However, erythrocytes and the liver do not utilize ketones [61].

The concentration of postprandial blood KB is 0.1–0.2 mM and varies depending on carbohydrates availability [18]. A blood KB concentration of > 0.5 mM is a commonly used threshold qualifying a state of NK [62]. It is quite safe, as the concentration of KB is far lower than the concentration seen in diabetic ketoacidosis [21, 63]. The energy metabolic reprograms from using glucose as a fuel source to using fatty acids and KB results in greater metabolic flexibility and efficiency of energy production. 100 g of acetoacetate generate 9.4 kg ATP, and 100 g of β-HB yield 10.5 kg ATP, while 100g of glucose produce only 8.7 kg ATP [60, 64].

In NK formed by metabolic reprogramming, KBs exert large effects by modulating carbohydrate and fat metabolism [23]. KBs are not only fuel but also potent signaling molecules with major effects on cell and organ functions. KBs regulate the expression and activity of many proteins and molecules associated with health and aging [65]. They also activate pathways that enhance intrinsic defenses against oxidative and metabolic stress, and remove or repair damaged molecules [42]. These include fibroblast growth factor 21 [66, 67], ADP ribosyl cyclase [68], nicotinamide adenine dinucleotide (NAD+), etc [69]. KBs have a profound effect on systemic metabolism by influencing the major cellular pathways that bolster mitochondrial function, antioxidant defenses, and stress resistance while upregulating autophagy. Moreover, KBs stimulate the expression of the gene for brain-derived neurotrophic factor, with implications for brain health; psychiatric and neurodegenerative disorders; and emotional disturbance [42]. Preclinical studies show consistent the disease-modifying efficacy of NK on a wide range of chronic disorders, including diabetes, obesity, neurodegenerative brain diseases, inflammatory diseases, and cancers [29].

NK and metabolism

The favorable effects of NK on caloric intake, lipid parameters, glycemic indices, and insulin sensitivity render it a therapeutic option in a variety of conditions, such as diabetes, obesity, and other metabolic disorders. The metabolic actions of KBs can alter fuel selection through attenuating glucose utilization in peripheral tissues, anti-lipolytic effects on adipose tissue, and attenuation of proteolysis in skeletal muscles [70].

Diabetes is a complicated metabolic syndrome [71]. NK is significantly beneficial in lowering oral glucose tolerance test, controlling hyperglycemia, reversing insulin resistance, improving glycemic control (glycated hemoglobin), eliminating/reducing diabetic medications, increasing high-density lipoprotein cholesterol (HDL-C), reducing hunger, and causing weight loss in overweight and obese individuals with type 2 diabetes [72, 73]. Moreover, limiting both proteins and carbohydrates can reverse diabetic nephropathy [74]. Among patients with diabetes

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treated with insulin and insulin secretagogues, KD may increase the risk of hypoglycemia, which can be solved by modifying the drug dosage [73]. Furthermore, KBs are being proposed as super-metabolic fuel, and KD is currently regarded as an apt dietary therapy for diabetes [75].

Sodium-glucose co-transporter-2 inhibitor (SGLT2i) is a novel diabetes drug that inhibits the kidney transporter, which reabsorbs 90% glucose [76]. This reduces the reabsorption of glucose and promotes glycosuria. SGLT2i has a good insulin-independent hypoglycemic effect and leads to significant caloric deficiency and weight loss [77], mimicking fasting-induced metabolic reprogramming of fuel energetics and amelioration of insulin resistance with KB utilization. KBs are commonly observed in patients treated with SGLT2i [78].

In addition to the hypoglycemic effect, SGLT2i has also been proven to have a protection effect on the cardiovascular and renal systems. SGLT2i is even better for heart failure than antihypertensive drugs [79]. The main mechanism of cardiac protection is to improve cardiomyocyte metabolism, improve ventricular load, and reduce cardiomyocyte necrosis and myocardial fibrosis [80]. KBs compete with free fatty acids and glucose for metabolic oxidation in cardiac mitochondria [81, 82]. KBs have multiple heart-protective effects: (1) it maintains mitochondrial integrity by producing less reactive oxygen species, which is the best substrate for all tissues, including the heart [83, 84]; (2) it stabilizes cell membrane potential and provides an antiarrhythmic effect; (3) it blocks the hypertrophic transcription pathway by inhibiting histone deacetylase [85, 86]. Obesity and insulin resistance are risk factors for cardiovascular events [87]. The main mechanism for weight loss is increased fat oxidation as well [88]. SGLT2i can provide kidney protection for diabetic patients with or without diabetes-related kidney disease [89]. It is also presumed to be due to the metabolic reprogramming to replace glucose and fatty acids with KBs as the preferred energy source, providing more energy-efficient oxygen consumption while improving the oxygenation of kidney tissues [90, 91].

Obesity is a major clinical and public health problem leading to diabetes, dyslipidemia, and hypertension, as well as increased cardiovascular and overall mortality. The KD has shown greater weight loss as compared with other balanced diets. The possible mechanisms involved are controlled hunger due to the higher satiety effect and the direct appetite-suppressing action of KBs, increased lipolysis, increased metabolic costs of gluconeogenesis, and improved regulation in the circulating the level of ghrelin and leptin that control appetite [92, 93].

NK can improve cardiovascular risk parameters through improvement in hepatic, intravascular, and peripheral metabolism of lipoproteins and alterations in fatty acid composition. NK may confer the unique metabolic benefits, such as lowering blood pressure and diminishing resistance to insulin without any adverse impact on renal or liver functions [94].

Thus, NK is beneficial in alleviating metabolic disorders (obesity, insulin resistance, hypertension, or a combination of these disorders). Also, KD is not only beneficial but also probably life-saving in diseases involving glucose metabolism and transport, such as glucose transporter protein deficiency and pyruvate dehydrogenase deficiency [95, 96].

NK and nervous system

NK is recognized as being neuroprotective and good for epilepsy, autism spectrum disorders (ASD), Alzheimer's disease (AD), and emotional disturbance. KD originates from the fasting treatment of epilepsy, which aims to provide energy for the brain. Brain KB levels are positively correlated with blood KB levels [97]. Although there is an increased availability of anticonvulsants recently, it has become more commonly used in academic centers throughout the world even in the early course of epilepsy [27]. Regarding the need for growth and development, KD can ensure that the basic nutritional intake is more suitable for children than fasting. Success in seizure control generally takes 1–2 years, which tends to relate to the level of ketosis [27]. The effect of NK on epileptics is not only in the typical age range (5–10 years) but also in other age groups, including adults [98].

In NK, KBs can protect brain cells, reduce free radical damage, and improve mitochondrial function. It can inhibit nerve excitation, promote and optimize the expression of neurotransmitters like brain-derived neurotrophic growth factor, and regulate intracerebral circulation [99]. The most plausible reason is because of the increased formation of KBs by which NK suppresses seizures [45]. β-HB is structurally similar to gamma aminobutyric acid (GABA) and may also have direct anticonvulsant or antiepileptogenic effects [30, 100].

NK affects various neurological conditions characterized by glutamate receptor-mediated excitotoxicity, including AD [101]. The brain in AD shows glucose hypometabolism but may utilize KBs for energy production without a decline in aging [102]. Evidence from a rat model suggests that NK can attenuate seizure-induced neuronal injury via autophagy [103]. NK can also improve cognitive-behavioral outcomes, decrease β-amyloid deposition, and prevent hyperphosphorylated tau pathologies [104]. A meta-analysis indicated that NK induced by medium-chain triglycerides may improve cognition in patients with mild cognitive impairment and AD [105].

The chronic activation of anabolic cellular pathways

and metabolic conversion disorder resulting in a deficit in GABAergic signaling and neuronal network hyper excitability may contribute to alterations in gene expression that result in ASD [106]. KD, through inducing NK and improving metabolic health, may ameliorate developmental neuronal network abnormalities and consequent behavioral manifestations in ASD [107].

Preclinical studies, case reports, and case series have demonstrated the antidepressant and mood-stabilizing effects of NK. The molecular basis may involve the multiple physiological processes of mood disorders, primarily including increased cAMP-response, element-binding protein phosphorylation, neurotrophic effects, endorphin release, glutamate/GABA transmission, monoamine levels, insulin dysfunction, and inflammation [22, 108].

NK and tumor

There is a growing awareness regarding the fact that the metabolic phenotype of cells within tumors is heterogeneous. In general, tumor cells lack genomic and metabolic flexibility, and these cells depend on anaerobic oxidation of glucose to a large extent. The rates of metabolizing glucose and lactate are much higher than their non-tumor equivalents [109, 110]. Tumors undergo a series of metabolic changes characterized by the Warburg effect, including (1) enhanced aerobic glycolysis; (2) increased glucose uptake and consumption; (3) enhanced lipid and protein synthesis; (4) increased glutamine uptake and catabolism, which are conducive to tumor malignant proliferation, invasion, metastasis, and adaptation to an adverse living environment. Designed to lack key mitochondrial enzymes, tumors are unable to use KBs as energy sources [111, 112].

In contrast to tumor cells, normal cells also depend on glucose metabolism, yet they have the flexibility to use KBs during caloric restriction. Targeting the metabolic differences between tumor and normal cells is regarded as a novel anticancer strategy. During NK, the body cells depend on lipid oxidation and mitochondrial respiration. KBs, as the main source of energy, limit the use of glucose and impair energy metabolism in cancer cells, inhibiting their growth and rendering them susceptible to clinical treatments. Based on the fact that NK is good for tumors, a nutritionally balanced KD can be used as supportive treatment for the tumor [109, 113].

Preclinical evidence

The definite effect of protecting brain cells and inhibiting nerve excitement triggered KD anti-tumor researches on gliomas, and then the studies extended to other brain tumors and other system origins. Preclinical studies have shown that NK has profound effects, such as preventing cancer initiation, inhibiting tumor growth, enhancing the effects of radiation and chemotherapy, and prolonging survival in lung [111], gastric [114], colorectal cancers [115], to name a few.

A recent analysis including 29 animal and 24 human studies demonstrated that the majority of animal studies (72%) yielded evidence for the anti-tumor effect of KD [116]. The high glycolytic rate resulted in resistance to radiation therapy and cancer progression. Performing KD on the transplanted tumor model of lung cancer resulted in the enhanced efficacy of radiotherapy by improving oxidative stress [111]. The mechanisms observed in vivo are: (1) the improvement of DNA repair in normal non-tumor cells; (2) the inhibition of tumor cell repopulation through the modulation of the PI3K/AKT/mTOR pathway causing a downstream of insulin and insulin-like growth factor-1; (3) the redistribution of normal cells into more radio-resistant cell cycle phases; (4) the normalization of the tumor vasculature; (5) the increase in the intrinsic radio-resistance of normal cells [113].

Shi Yujiang's team found that hyperglycemia could significantly inhibit the activity of the AMP-activated kinase in vivo, destroy the formation of apparent anticancer modification, and increase the risk of cancer. A lower blood glucose level during NK could reduce the risk of cancer [117]. NK might suppress the progression of cancer and the accompanying systemic inflammation without any adverse effects on weight gain or muscle mass in colon tumor-bearing mice, which might help to prevent cancer cachexia [118]. Inhibition of NAD+ metabolism can lead to DNA damage and tumorigenesis, while restoring NAD+ concentrations can prevent DNA damage and tumorigenesis [119]. A study of the rat model showed that KD could significantly increase the proportion of NAD+/NADH, suggesting that NK can improve various brain dysfunctions, metabolic disorders, and anti-tumor mechanisms by increasing NAD+ [120]. NK can also limit the activity of glutathione peroxidase, to improve the efficiency of CD8+ tumor-infiltrating lymphocyte cytotoxicity in tumor tissue through the recombination of intestinal flora and immune metabolism [121]. Byrne et al. started KD on mice after liver tumor initiation and found that while NK had marked protective effects against liver tumorigenesis, it could not stop the progression of established liver tumors [122].

In another report, Feyter et al. found that rat gliomas could oxidize KBs and upregulate KB transport when fed with a KD. It contradicts the hypothesis that brain tumors are metabolically inflexible [123]. They carefully analyzed β-HB metabolism and found that glioma tissue in vivo took up β-HB and metabolized it to glutamate. Rat gliomas even could upregulate β-HB transporters when they were grown in the NK environment. That may be attributed to the fact that KB metabolism differs between species, and in this

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case, between rat and man [31].

Clinical evidence

NK could potentially inhibit the growth of malignant cells, including neuroblastoma, pancreas, prostate, stomach, colon, brain, and lung cancers, and it may even increase survival time [124]. Current clinical researches on the effects of NK on tumors are mostly limited to small pilot studies or case reports and mainly focused on cancers with poor prognoses, with NK as part of the auxiliary support therapy [125].

Nebeling et al. reported a decrease in glucose uptake at the tumor site in patients with malignant astrocytoma tumors, which led to significant clinical improvements in the quality of life [126]. The first prospective clinical trial on KD in recurrent malignant glioma demonstrated that KD could be safely applied to patients and might increase the efficacy of anti-angiogenic therapies in a mouse xenograft model [127]. Prospective studies of KD, combined with radiotherapy and chemotherapy, suggest that it is feasible and safe as a radiation sensitizer for glioma during radiation and chemotherapy treatment [128], as an adjuvant to standard chemoradiation treatment of glioblastoma multiforme [129], and also as a synergistic regimen to chemotherapy in stage IV rectal cancer patients [130].

There are just two randomized controlled trials (RCTs) that are conducted to determine the effects of NK on cancer, and both are cancers closely related to obesity [131]. One is an RCT (NCT03171506) of ovarian or endometrial cancer, which showed that NK could improve physical function, increase energy, and diminish specific food cravings [131]. Another RCT suggested that among patients with locally advanced breast cancer receiving neoadjuvant chemotherapy, fat mass and body weight decreased to a much greater extent, and overall survival was longer in the KD group after 30 months follow-up [132]. KD prescription varied widely between studies and was described only rudimentarily in most papers [125].

The influence of NK on overall survival is still inconclusive until now. Patients with malignant tumors are usually accompanied by malnutrition (40%–80%), systemic inflammation, hypoimmunity, and other concomitant symptoms. The unique energy supply mode and anti-inflammatory effect of NK make KD or BHR a supportive therapy for anti-tumor treatment. The difficulty is that the routine administration of hormones and intravenous infusion of glucose are often needed for clinical treatment of tumors, which will probably affect the maintenance of NK. A retrospective study on glioblastoma multiforme indicated that KD reduced serum glucose levels significantly, even in conjunction with high-dose steroids [133]. The researchers focused more on patients incapable or unwilling to cook for themselves or relying on formula foods due to swallowing difficulties and were more committed to finding a suitable diet as nutrition support [134]. Larger prospective trials to confirm this relationship are warranted.

NK and immune system

Immoderate diets can promote chronic inflammation leading to numerous diseases, such as cancer; diabetes mellitus; cardiovascular and chronic renal diseases; and autoimmune and neurodegenerative disorders [135]. High glucose intake can exacerbate autoimmunity through growth factor-β cytokine activation [136].

Preclinical data suggest that KDs affect inflammation and, consequently, cytokine release. By using a rat model in a study regarding fever, Dupuis et al. found that the animals that achieved NK showed less fever and low proinflammatory cytokine levels [137]. NK exerts anti-inflammatory actions via the promotion of microglial ramification [138], increasing the relative abundance of putatively beneficial gut microbiota while reducing putatively proinflammatory taxa [139].

Recently, it has been found that NK protects mice from lethal influenza A virus infection as a result of an expansion of γδ T cells in the lungs, which improve barrier functions, thereby enhancing antiviral resistance [140, 141]. A retrospective case-control study reported that in a group of 125 consecutive adults with epilepsy, baseline immunosuppression did not worsen with KD [142]. Furthermore, a domestic clinical study found that flexible BHR-induced NK could increase the probiotic proportion in intestinal flora of chronic urticaria patients and, as a result, improve the symptoms of chronic urticaria, especially in chronic idiopathic urticaria [14]. Goldberg et al. identified that NK could block interleukin-1β in neutrophils and alleviate urate crystal-induced gout without impairing immune defense against bacterial infection in mice and humans [143]. Multiple sclerosis (MS) is a common inflammatory disease. Preclinical data suggest that KD may modulate immunity in the mouse model of MS [144]. A single-arm prospective study enrolling 20 subjects with relapsing MS indicated that KD reduced the serologic levels of proinflammatory adipokines and alleviated fatigue [145]. However, the first RCT investigating the effects of KD on disease progression of MS (n = 111) is still enrolling [146].

NK and lifespan

Aging may be a predominant risk factor for major diseases. Moreover, dietary interventions are simple, non-invasive methods that can be utilized to improve health and lifespan. Preclinical evidence demonstrates that KDs can extend longevity, improve health, and

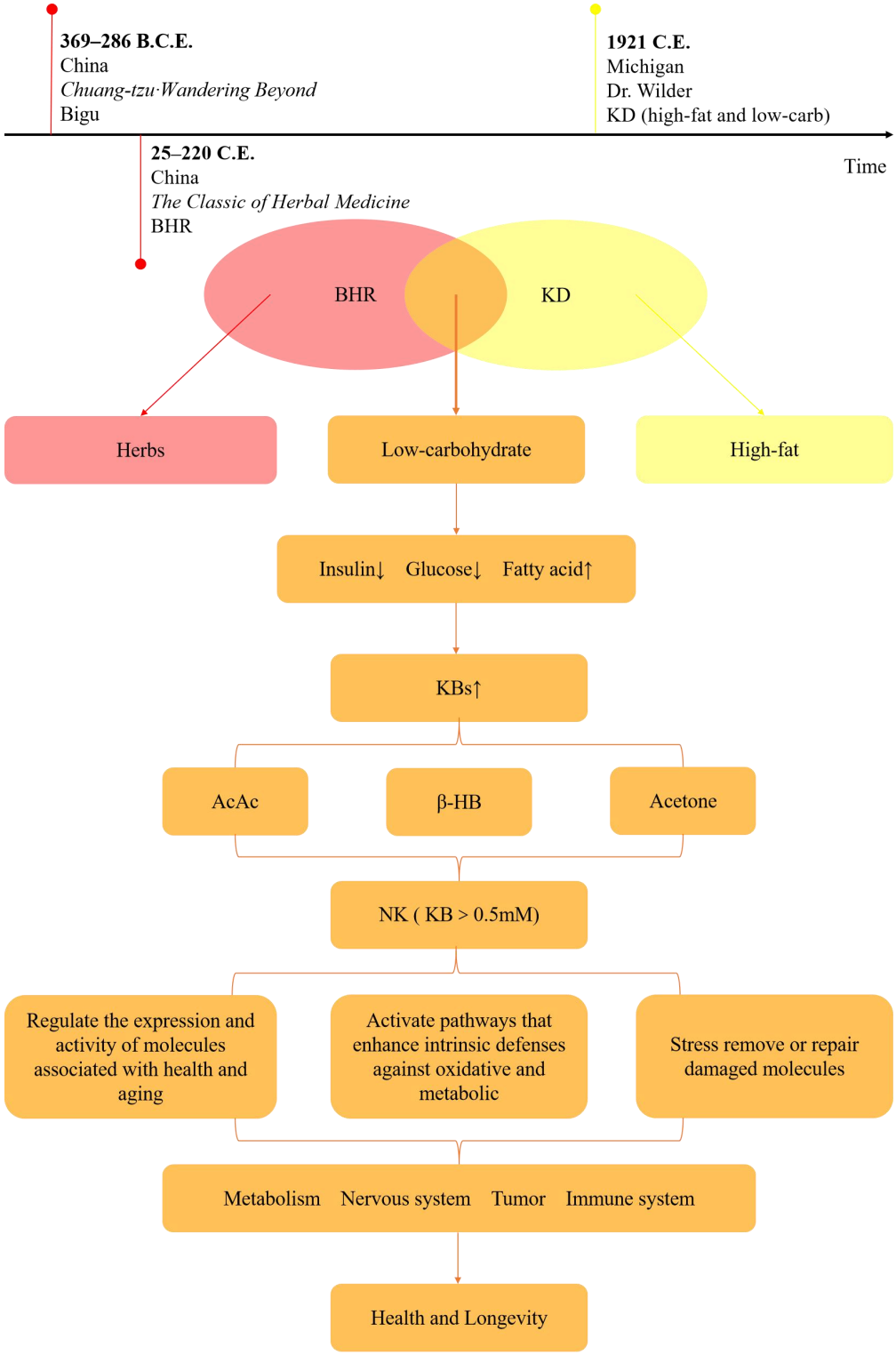

Figure 1 Bigu-herbs regimen and ketogenic diet achieve the same purpose—ketone body. BHR, Bigu-herbs regimen; KD, ketogenic diet; KB, ketone body; NK, nutritional ketosis; β-HB, β-hydroxybutyrate; AcAc, acetoacetate.

preserve physiological functions in mice. The known mechanisms are the following: (1) KDs can increase protein acetylation levels; (2) regulate mTORC1 signaling in a tissue-dependent manner [147]; (3) upregulate peroxisome proliferator-activated receptor-α target genes that cause proliferation of

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peroxisomes [148]; (4) render cells more resilient against DNA damage and metabolic insults via NAD+-related mechanisms. NAD+ is a marker of cellular health and a substrate for enzymes correlated to longevity and DNA damage repair [149]. A large-scale prospective cohort study (n > 135,000) showed that nutritive carbohydrates increase human mortality, whereas dietary fat reduces it [150].

Side effects and contraindications

Adverse events attributed to KDs are generally minor (grade 1–2) [125]. The probability of benefits seems greater than that of the disadvantages, such as causing serious side effects when offering KDs to cancer patients [116]. The common side effects are mild and include acidosis (insulin dysfunction), constipation, and insomnia. The less common ones are growth inhibition (more significant at young ages), kidney stones (6%), and hyperlipidemia [27]. Short-term effects include dehydration, anorexia, nausea, constipation, acidosis, and hypoglycemia. Long-term effects include severe hepatic steatosis, disruptions in lipid metabolism, mineral deficiencies, nephrolithiasis, and increased redox imbalance [75]. The increase in cholesterol may be caused by a decrease of apolipoprotein B, the major serum carrier of cholesterol, which can be reversed by adjustments to the diet (e.g., increased protein and polyunsaturated fats) [151].

Most of the adverse effects may be preventable and treatable. Increasing meal frequency may improve diet tolerance [46]. There may also be an increase in serum uric acid levels when this fat catabolic product increases concentration in the blood but is not excreted efficiently. Sufficient fluids and oral alkalis are prescribed to reduce the incidence of kidney stones. Ample sleep, high-fiber diet, and supplementation of vitamins and minerals are recommended to overcome the side effects [75].

Some lipid metabolic disorders, such as pyruvate-carboxylase deficiency, defects of fatty acid oxidation, carnitine deficiency, and mitochondrial disorders, are thought to be contraindications to KD [152].

Predicament and prospect

Both BHR and KD could promote KBs production by limiting carbohydrate intake, resulting in an energy metabolic reprogramming to achieve a state of NK. Insufficient carbohydrate intake leads to a decrease in blood glucose and insulin, an increase in insulin sensitivity and fatty acid mobilization, and consequently promote the formation of KBs. NK has a beneficial effect on metabolism, the nervous and immune systems, and the body's anti-tumor mechanisms, thereby promoting health and aging (Figure 1).The specific diet plan of KD is uncertain and related research is still in the clinical stage. The effect of NK on epilepsy and weight loss is relatively demonstrated and has been in clinical application. However, further studies on the role of NK in the treatment of diabetes, AD, tumor, autoimmune diseases, and other chronic diseases still mostly require high-quality clinical trials. KD- and BHR-induced NK provide a safe and efficient approach to the study regarding its effects on aging and potential treatment of various diseases. Hopefully, further studies will enable us to understand how NK can be implemented and how it can complement established treatments.

In terms of compliance, patients are more willing to accept natural therapies without chemical drugs. On another note, it seems difficult to strictly apply a long-term KD in the Chinese cultural context because their staple foods (rice/noodles) mainly consist of carbohydrates. In terms of security, there is still a lack of data to support long-term KD [153]. Meals must be carefully chosen according to one's illness, nutrition, etc., to formulate an individual ketogenesis plan. Applying KD as part of a treatment plan requires a specially trained dietitian and medical team and is often difficult to reimburse [154]. Traditional BHR experts with rich practical experience could be referred to, however.

In the future, joint studies may be conducted on multiple targets to identify mechanisms, and the clinical investigation and transformation of animal researches will be carried out to develop more rational and practical regimens, more ketogenic products, and even more advanced methods, such KB-based intravenous and oral preparations for clinical use.

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