

A Critical Review of the Association between Nutrition and Health in Modern Chinese Diet

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Abstract Cardiovascular diseases (CVDs), obesity, diabetes, cancers and other chronic diseases are becoming main contributors to the global burden of disease, even as nutritional deficiencies are receding as leading contributors to mortality and disability. Diet is closely related to nutrition and health, which has been extensively investigated as risk factors for major chronic diseases. The past two decades have witnessed rapid changes in dietary pattern in China. However, a critical thinking of Chinese diet behind these changes is less emphasized. Given the causal relationship between nutrition and disease, lack of adequate nutrition and unhealthy diet habits might be responsible for the high incidence of chronic diseases in China in recent years. To this end, we will critically review some open problems in current diet compositions and the importance of regular mealtimes. The intake level of dietary supplements in China will also be discussed.

Keywords: chinese diet, nutrition, health, chronic diseases

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1. Introduction

In recent years, health care or self-management (taking care of your own health) is gaining more and more attention globally because of the baby boom generation and aging population. A publication of the US Public Health Service agenda laid out guidelines that support the realization of a vision of improved health, of which diet changes are one of the most effective approaches to prevent nutrition-related illnesses occurring at any age of life [1]. Food nutrition refers to the general term for the heat energy and nutrients that the human body can obtain from the food. According to the characteristic of nutrients, source of nutrition is classified into 3 categories: (1) fresh food (agricultural products), (2) cooking food and (3) processed food.

China has achieved outstanding economic progress and high levels of education during the past years, and Chinese diet has also evolved rapidly, along with these changes in economy and related social activities [2]. Traditionally, Chinese diet includes fruits, vegetables and cereals with few animal foods. Many researchers believe that this diet is the most beneficial to health when ingested adequately [3]. Nowadays, animal foods including meat, eggs, aquatic

products, and milk are becoming very popular in both urban and rural areas. Beyond that, a growing number of people are pursuing a balanced diet that provides all the nutrients in sufficient quantities to meet the nutritional needs of the body. However, it is difficult for a large majority of people to achieve and maintain a balanced diet. For example, the recommended calcium intake for adults over 18 years of age is 800 mg per day according to the Chinese Dietary Reference Intakes Summary [4]. It was surveyed that the percentage of adults achieving the Chinese dietary reference intake on calcium was only 4.3% [5]. Eating a well-balanced diet appears to be just a concept for most people and inadequate nutrient intake is still a widespread problem.

It is important to know that a large quantity of nutrients is lost or changed in cooking and processed foods to some extent. Any forms of cooking will destroy some nutrients in the food, but the determinants are the volumes of water used in the cooking process, as well as the cooking time and temperature [6]. There are some nutrients such as vitamin C, protein and micronutrients that are extremely unstable under high temperature and are readily decomposed or metabolized into other substances [7,8,9]. Besides that, food processing such as malting, drying, milling, and extrusion is also shown to have major effect on nutrients content [10,11]. These make it difficult

to guarantee the intake of necessary and sufficient nutrients from the diet. Moreover, the flavor and taste of the food after cooking or processing have been greatly improved, which may lead to excessive intake of unhealthy ingredients, thereby harming health. A study showed that a number of school students consumed high amounts of sugars, saturated fat and sodium through processed beverages, milk and Ramen in their diet [12]. As a result, some chronic diseases including obesity, diabetes, and cardiovascular diseases (CVDs) resulted from metabolic alterations [13,14], have dramatically increased in recent years [15,16].

In the current study, we will provide a critical review of the relationship between Chinese diet and nutrition, as well as dietary factors in increasing incidence of diseases, attempting to show people a positive implication to adjust their diet. Considering the prevalence of health-care food, the intake level of dietary supplement in China and its role in nutritional intervention and health promotion will be discussed.

2. Diet Composition in Relation to Nutrition and Health

2.1. Fruits

Fruits have been considered as an important part of a healthy diet as prolific source of nutrients (vitamins, minerals, folate, and dietary fiber) and bioactive substances (polyphenols, anthocyanins, flavonoids, and essential oils) is present in fruits [17,18]. The consumption of fruits should be encouraged, which may be useful to enhance fruit concentrations of nutrients and bioactive substances. It has been documented that intake of fruits has been associated with lower risks of developing chronic diseases and a wide range of cancer types [19,20]. For example, cranberry can reduce the incidence of urinary tract infections in women [21] and grape has favorable effects on cardiovascular risk markers [22]. More fruits and their health benefits are described in Table 1.

Table 1. Summary of familiar fruits in China with reported health benefits

Fruit	Place of origin	Sample	Major compound	Health benefit	Reference
Kiwifruit	Shaanxi, China	Whole fruit	Protocatechuic, <i>p</i> -hydroxybenzoic, vanillic, caffeic, syringic, <i>p</i> -coumaric, ferulic, anisic acids	Antioxidant, against oxidative DNA damage <i>in vitro</i> and <i>in vivo</i>	[23,24]
Banana	Hainan, China	Peel, pulp	β -sitosterol, malic acid, 12-hydroxystearic acid, succinic acid, gallic acid, catechin, epicatechin, tannins, anthocyanins, lutein, β -carotene, α -carotene, violaxanthin, auroxanthin, neoxanthin, cryptoxanthin	Antioxidant, antimicrobial, reducing the risks of chronic degenerative disorders	[25,26,27]
Mango	Hainan, China	Peel, pulp	Malic acid, neoxanthin, violaxanthin, lutein, β -carotene	DPPH radical-scavenging, antioxidant, hepatoprotective effect	[28,29]
Litchi	Guangdong, China	Pulp	Gallic acid chlorogenic acid, catechin, caffeic acid, epicatechin, rutin, quercetin, kaempferol; polysaccharides	Antioxidant, protective effect on cardiovascular health	[30,31,32]
Apple	Shandong, China	Pulp, peel	Chlorogenic acid, coumaryl quinic ester, catechin, epicatechin, phloretin glucoside, quercetin	Free radical scavenging, antioxidant, decreasing the risk of heart disease, lung cancer, asthma, and diabetes	[33,34]
Bayberry	Zhejiang, China	Pulp	Cyanidin-3- <i>O</i> -glucoside, rutin, myricetin	Free radical scavenging, antioxidant, reducing oxidative stress	[35,36]
Papaya	Hainan, China	Seed, leave	Benzaldehyde, benzyl nitrile, benzyl isothiocyanate	Antifungal, antioxidant, healing of wounds, reducing CVDs risk, anti-inflammatory, anti-tumor	[37,38]
Cantaloupe	Xinjiang, China	Pulp	Lutein, β -carotene	Antioxidant	[39]
Strawberry	Hebei, China	Puree, pulp	Ellagitannin, ellagic acid glycoside, ellagic acid, catechin, proanthocyanidin, <i>p</i> -coumaroyl glycoside, quercetin-3-glucoside, ascorbic acid, caffeic acid, gallic acid, ellagitannin,	Antioxidant, anti-inflammatory, cardioprotective, anti-metabolic syndrome, anti-obesity, antidiabetic, anticancer, neuroprotective, antimicrobial	[40,41]
Pomegranate	Sichuan, Shanxi, China	Peel	Chlorogenic, caffeic, <i>p</i> coumaric, syringic, gallic, sinapic, cinnamic acid, vanillic, ellagic, ferulic, procyanidins, epicatechin, anthocyanins, quercetin, catechin	Antioxidant, cardiovascular health-promoting effects	[42,43]
Citrus fruits	Guangdong, Hainan, China	Pulp, peel, seed, core, membrane	Hesperetin, quercatagetin, narirutin, hesperidin, naringin, neohesperidin, naringenin, coumarin, 5-Geranyloxy-7-methoxycoumarin,	Antioxidant, anti-atherogenic, anti-inflammatory, anti-tumor, inhibition of blood clots, antimicrobial	[44,45]

Now people in China may have better access to various fruits harvested in any season because of the development of food technology and prosperity of import trade. It is worth mentioning that citrus fruits have been popular in China for centuries, which is attributed to the fact that they can provide good taste and low cost. Moreover, relatively high content of vitamin C and polyphenols in citrus fruits has attracted intense interest of researchers and consumers during the past years. They can act as antioxidants to protect the body's tissues against oxidative stress and diseases related to oxidative damage such as CVDs and cancers [46]. In general, most people in China has realized that intake of fruits in the diet is crucial to long-term health care and it is suggested by Chinese society of nutrition that we should consume fresh fruits of different kinds as possible as we can.

2.2. Vegetables

Vegetables in modern Chinese diet likewise provide a significant part of nutrition, as they are important sources of nutrients (minerals and vitamins), dietary fiber, and phytochemicals [47]. In addition to vitamins, the presence of phytochemicals (polyphenols, glucosinolates, carotenoids, sterols and saponins) in vegetables has been considered to be of vital nutritional value in preventing chronic diseases such as CVDs, diabetes and cancers [48,49]. Previous studies have shown that individuals who eat daily five or more servings of vegetables have

approximately half the risk of developing various cancers [50].

However, the difference with fruits is that most vegetables need to be cooked before being consumed in order to make them more appetizing or safer to eat. Overall, people enjoy the boiled vegetables in the south of China while people prefer stir-frying vegetables in the north of China. The ingredient content of vegetables prepared with heat may change to varying degrees, particularly the heat-sensitive vitamins and phytochemicals [51]. Miglio *et al* showed that three common cooking practices (boiling, frying and steaming) have obvious effect on phytochemical contents (polyphenols, glucosinolates, ascorbic acid, and carotenoids) and total antioxidant capacity of selected vegetables, containing carrots, courgettes, and broccoli [52]. Another study reported that effect of five domestic cooking methods including microwaving, boiling, steaming, stir-frying, and stir-frying/boiling on the nutrients and health-promoting compounds in broccoli, indicating that all cooking treatments, except steaming, led to significant losses of vitamin C and chlorophyll and significant decreases of soluble sugars and total soluble protein [53]. Similar reports are shown in the following Table 2. Additionally, in order to make vegetables more appetizing, high consumption of edible salt and sodium glutamate involved high-sodium intake in these cooking methods, especially in the north of China, is linked to the development of hypertension and CVDs [54,55].

Table 2. Effect of different cooking methods on nutrients in vegetable

Vegetable	Cooking method	Specific influence	Reference
Namkeen dalia	Boiling	The 40.2 percent loss of iodine	
Chapati	Roasting	The 10.5 percent loss of iodine	
Parantha	Shallow frying	The 6.5 percent loss of iodine	
Poori	Deep frying	The 10.4 percent loss of iodine	[56]
Chhole	Pressure cooking	The 51.0percent loss of iodine	
Upma	Microwaving	The 27.1 percent loss of iodine	
Broccoli	Boiling, steaming, microwaving	High loss of chlorophylls, vitamin C, increase of pheophytins	[53,57]
Spinach			
Squash			
Leek	Boiling, steaming, microwaving	High loss of chlorophylls, increase of pheophytins	[57]
Peas			
Green beans			
Cauliflower			
Cabbage	Steaming, boiling, microwaving	Great loss of antioxidants	[58]
Choy-sum			
Green asparagus	Boiling, steaming, microwaving	Loss of chlorophylls, carotenoids, total polyphenols	[59]
Some wild green leafy vegetables	Boiling	Vitamin C content decreases considerably	[60]
Pepper			
Squash			
Green beans			
Peas	Microwave and conventional cooking methods (boiling, steaming)	Affect total phenolics content significantly, loss of total antioxidant activity	[61,62]
Leek			
broccoli			
spinach			
Cauliflower			
Peas			
Spinach	Microwave, boiling, pressure cooking	A significant decrease in total phenolic content	[63,64]
Swiss chard			
Garlic	Griddling, boiling, pressure-cooking, frying, baking	High loss of the ABTS radical scavenging capacity	
Green bean			[65]
Celery			
Carrot	Griddling, microwaving, baking	A low ABTS radical scavenging capacity	

Taken together, it was showed that two popular Chinese cooking methods including stir-frying and boiling could cause great losses of nutrients and bioactive components in vegetables. Therefore, a cooking method for each vegetable must be preferred to preserve the nutritional and physicochemical qualities, and proper use of condiments for a healthy diet is more likely to reduce the risk of CVDs.

2.3. Cereals

Cereals grains including barley, oats, wheat, rice and rye, are staple foods in the diet of many populations, especially in developing countries, as they can provide essential nutrients such as carbohydrate energy, dietary fiber, protein, unsaturated fatty acid and a variety of phytochemicals and micronutrients [66,67]. Rice, is one of the most important staple foods in China, particularly in the southern parts, while wheat and their products have played the role of traditional staple food for thousands of years in the northern China [68,69].

However, based on previous studies, it has been shown that excessive of intake of white rice was associated with a significantly increased risk of type 2 diabetes, especially in Asian (Chinese and Japanese) regions [70,71]. In addition, for extended shelf life and consumer appeal, rice and wheat have to undergo different degrees of refining and milling process that will cause a reduction in fiber and essential micronutrients content [72]. Increasing consumption of these highly polished rice and refined grain (wheat) may lead to an extremely high gastrointestinal (GI) value and high prevalence of diabetes and CVDs [72,73,74].

Accordingly, more and more people are inclined to consume the whole grains because all of the nutrients are retained in the form of whole grains and the whole grain foods are believed to improve the quality of the diet. A number of evidences have shown that consumption of whole grains against the risk of many chronic diseases such as type 2 diabetes [75,76] CVDs and some cancers [77]. The health benefits of whole grains consumption may be due to their unique phytochemicals including carotenoids, phenolics, β -glucan, and γ -oryzanol that are complementary to those in fruits and vegetables when consumed together [78]. However, it is worth noting that many of the potential beneficial compounds in whole grains become unavailable during the refining process [79]. Previous studies showed that favorable lipid profiles and glycemic control were closely related to higher intake of whole grains, but not refined grains [80,81]. Thus, we should be prudent to distinguish whole-grain from refined-cereal-grain products for the prevention of chronic diseases.

2.4. Meats

Meat and processed meat products are regularly consumed in many regions of the world, providing unique eating satisfaction in the lifestyle of the modern society. They also offer high-value proteins and important nutrients such as long chain n-3 fatty acids, vitamin B family, essential trace elements and a number of other micronutrients [82,83,84]. Although there may be competition between feed and food resources or other environmental problems [85], it is estimated that the

demand for meat and animal-derived foods in the coming decades will continue to grow strongly in developing countries [86]. A rich variety of meat and meat products involved in pork, beef, lamb, poultry and fish are produced in China annually. Among them, the consumption of red meat (mostly from mammals) accounts for a larger proportion than white meat (mostly from poultry and fish). However, the red meat is deemed to play a role in both arguments for risks and benefits⁸⁷. The intake of higher amount of red meat than white meat is associated with an increased risk of chronic diseases, but it remains unclear whether the red meat intake is involved in mortality [88,89].

Influenced by the strong food culture and traditional Chinese cooking techniques, pursuit of gourmet food never seems to be interrupted. Toward this end, meat and meat products have been gone through a series of cooking treatments and processing methods. The cooking operation is a procedure usually applied prior to consumption, especially for meat and meat products, resulting in better aroma and the cooked meat is more tender when compared to the raw one. However, cooking methods also affects the nutritional value of meat due to changes in certain ingredients. Heterocyclic aromatic amines are one of the mutagenic compounds formed naturally during cooking of meat and fish [90], which have been positively associated with carcinogenicity in several epidemiological studies [91,92]. Moreover, a previous study showed that different cooking methods (hot plate, boiling, microwave, deep fat frying and oven cooking) caused 10% decrease in the amount of mineral component of beef steaks [93,94]. Yingqiu Li *et al* reported that pre-frying and extended cooking time significantly increased lipid oxidation and fat loss of stewed pork [95]. Herein, a traditional concept in Chinese medicine, “Shanghuo” is more akin to inflammation, without specific physiological indicators and varies from person to person, and it will bring about physiological dysfunctions if it is not treated on time [96]. It is very easy to obtain “Shanghuo” with the use of large number of additives such as cinnamon, star anise, and pepper during the cooking of meat, especially in hot weather. After that, it is necessary to administrate drug and food supplements to regulate the body to a normal state.

In the southwest of China, bacon (salt meat) is quite popular with local residents due to its distinct aroma and taste. Nitrate is added to the meat as an antioxidant to develop flavor and stabilize the red color, but it must be converted to nitrite to play these roles [97]. Epidemiologic and clinical studies have linked excessive nitrate and nitrite consumption in processed meat with increased risk of thyroid dysfunction and thyroid cancer [98], gastrointestinal cancers [99], gout [100], and chronic obstructive pulmonary disease in women [101]. Therefore, it should be emphasized to avoid consuming too many preserved foods containing nitrite, as well as other cooking foods with too many additives.

2.5. Wine

Chinese wine culture is broad and profound. Whether it is a festival, business or entertainment dinner, wine is an indispensable element on the table. Among the different

types of wine such as Chinese spirits, red wine, beer, yellow wine, fruit wine and health-care wine, Chinese spirits is the most common and popular one that is fermented from grain and usually has a high alcohol content. Although excessive alcohol consumption is undoubtedly harmful at several levels [102], consistent studies distinguishing between the consumption of spirits and wine/beer have found that only spirits increase mortality, not wine [103] and recent studies have provided further evidence that moderate wine consumption is associated with cardiovascular protection [104,105,106]. In last two decades, French Paradox described the low CVDs incidence and mortality of the French population despite their high dietary intake of saturated fats, which actually is attributed to wine consumption [107,108]. After that, in order to explain the inverse relationship between moderate wine consumption and the incidence of CVDs [109], many researchers showed their strong interest in exploring the components of wine [110]. It suggested that these effects may be ascribed to polyphenols (especially resveratrol), as well as other bioactive compounds exhibiting anticarcinogenic [111], hypotensive [112], antioxidant [113] and anti-inflammatory activities [114] in wine and beer. Therefore, this review is expected to serve as a reminder to those who might enjoy Chinese spirits or wine that moderate wine consumption, rather than excessive alcohol consumption, is beneficial to health.

2.6. Tea

Tea culture is also an important part of Chinese traditional culture. Tea is one of the most widely consumed beverages in China and there are a variety of teas such as green tea, white tea, black tea, oolong tea in the present market [115]. Among them, green tea accounts for the largest share of tea production in China [116], which is considered to have potential health benefits by traditional medicine in Asian regions [117,118]. In particular, it has been demonstrated that phenolic compounds in tea possess the bioactivity to influence the pathogenesis of many chronic diseases such as CVDs and cancers [117,119,120].

However, it was reported that tea had a remarkable effect on non-heme iron absorption in human body, which is attributed to the flavonoids present in tea [121]. Meanwhile, polyphenols in tea also has the ability to inhibit non-heme iron absorption in man, suggested by several studies *in vivo* [122,123] and *in vitro* [124]. For subjects at risk of iron deficiency, it is recommended to increase heme-iron intake (mainly present in fish and poultry) and to consume tea between meals instead of during the meals [125].

2.7. Snacks

Unhealthy dietary patterns including those that are high in total sodium, fat, and refined sugar have been linked to mid- and late-life diabetes [126], CVDs [127], obesity [128] and cancers [129]. The snack foods are frequently considered unhealthy and recommendations are often made to limit their consumption, mainly as part of an effort to control body weight but also to avoid intake of

saturated and *trans* fats [130]. In recent years, processed snack foods such as French fries, candy, ice cream, popcorn, and soft drinks, make up a large proportion of the average diet and have been increasingly consumed by children and adolescents in China [131,132]. These unhealthy snack foods may lead to chronic disease in adulthood begin early in life, and diet-related chronic disease risk factors [133]. Consequently, children and adolescents are suggested to eat less snacks with high energy and sweetener content; investigators should develop healthier snack foods including these high in fruits, vegetables and whole grains.

3. Association between Mealtimes and Health Promotion

A number of evidences have documented eating disorders in frequency and timing of meals, occurring across the globe in both developed and developing countries [134], increasing rates of eating disorder symptoms and behaviors in both children and adults with high mortality rates and high treatment costs [135,136]. Fundamentally, the circadian clock system programs daily rhythms and coordinates multiple behavioral and physiological processes, including sleep and eating [137]. Once the chronic disruption of the synchronous relationship between endogenous and exogenous circadian time may lead to the development of obesity and metabolic diseases [138], implying the frequency and timing of meals are associated with cardiovascular health outcomes [139].

In particular, the mealtimes play an important role in eating behavior. The food was usually eaten in three meals per day in China, consisting of breakfast, lunch and dinner, where lunch was the main meal [140]. Not eating at the right time or eating too much at a meal would result in the extension of the next meal time and a greater sense of satiety. Then, when you feel hungry, you have already missed the meal time. As a result, two forms of disordered eating including binge eating and night eating will appear [141], which is very common among young people in China. These unhealthy eating habits are often affected by social factors and are closely linked to metabolic diseases such as obesity [142], aging [143] and other chronic diseases [144]. Remarkably, breakfast plays a crucial role in energy balance and health-related quality of life. It was reported that regular breakfast had a significant effect on satiety over the entire morning and aspects of cognitive performance in adolescents [145]. Therefore, it is suggested to establish and adhere to a regular and healthy diet, especially for children and adolescents.

4. Intake Level of Dietary Supplements in China

A dietary supplement, also called health-care product in China, is any supplement taken orally that contains a dietary ingredient, involving products such as minerals, vitamins, herbs or botanicals, and amino acids. On one hand, many people cannot achieve adequate nutrients from

the diet, so they expect to strengthen nutrition from dietary supplements. In recent years, there has been an increasing need for dietary supplements, which reflects contemporary people's growing attention to health care. On the other hand, the over-saturated dietary supplement market in developed countries such as the US also drives the need for foreign market expansion, and Chinese market is a viable market for dietary supplement. Numerous literatures on dietary supplements reported that it could be used to improve overall health and well-being of an individual as well as reduce the prevalence of nutrition-related diseases. For example, vitamins and minerals have been identified as playing a potential role in prevention of bone diseases such as osteoporosis [146]. Milan Holecek reviewed that branched-chain amino acid (BCAA: valine, leucine and isoleucine) supplementation exhibited a favorable effect on the prognosis and treatment of hepatic disease [147]. Another study suggested that a low dietary intake of antioxidant vitamins increased the incidence rate of CVDs and cancers [148]. However, there are still some open issues to be discussed about the intake of dietary supplements in China.

First, health-care products are rarely popularized in rural areas while the intake level of health-care products by urban residents is relatively optimistic, but there are still some unscientific and blind worship phenomena, and some people even exaggerate the efficacy of health-care products. Thus, in order to obtain additional nutrients, people in both rural and urban areas should be educated about the safety and effectiveness of dietary supplements [149]. Second, at present, there are many varieties of health-care products with different functions on the market, and it is very challenging for consumers who lack relevant professional knowledge to find the right product for themselves [150]. In this regard, consumers should attempt to read the labels that provide important information such as ingredients, content, and shelf life of a specific product. Third, most of the main components in health-care products are synthesized and extracted, leading to their poor bioavailability in human body. For instance, commercial coenzyme Q10 (CoQ10) formulations available in the market are often of poor intestinal absorption [151]. The low oral bioavailability was mainly caused by the poor aqueous solubility in the GI tract [152]. Many investigators try to introduce novel delivery systems in order to improve the absorption rate in the body [153,154], but this also bring in more chemicals, which may cause adverse reactions to the human body [155]. Therefore, for a balanced nutrition, it is recommended that we should scientifically and rationally deal with dietary supplements at all times.

5. Challenges of the Status Quo

Since the rapid development of China's economy, along with the continuous development of urbanization and industrialization and the accelerated pace of life, Chinese diet has also undergone major changes. On the whole, the quality of Chinese people's meals has been significantly improved, and the malnutrition of children and adolescents has basically been solved. However, some health problems still exist. For example, the diet structure

varies in different regions, accompanied with some nutritional deficiencies, and the incidence rate of chronic diseases such as diabetes and obesity are on the rise. The reason is that blindly pursuing a good taste and stimulation on the tip of the tongue often overlooks some of the adverse effects caused by cooking methods and food processing. Moreover, given the China's historical and cultural background, it is estimated that some eating habits are difficult to change. Hence, only by constant education and promotion of healthy diets, combined with physical exercise, can improve the overall physical fitness of the Chinese.

6. Conclusion

Diet can be an important factor affecting not only health but also risks of diseases. A balanced and broadly varied dietary intake plays a critical role in human general health. This will require active collaborations between government, industry and academy; each of which possesses a concept of health promotion that can contribute to the realization of healthy diet for people in both rural and urban communities. Unfortunately, both Chinese traditional and modern diet composition have certain shortcomings, and it needs to be adjusted in order to achieve sufficient nutrients for the normal operation of the body. Meanwhile, proper mealtime behavior is also a guarantee of health, especially for children and adolescents. In addition, consumers should be scientifically educated about the safety and effectiveness of health-care products and investigators are definitely required to develop health-care products with relatively high bioavailability.

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Conflict of Interest

The authors have declared that no competing interests exist.

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