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Original Article

Effects of the Phytocompound Combination against Dysbiosis Induced by AGE-Rich High-fat Diet in Mice

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ABSTRACT

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Keywords
Advanced glycation end products
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Background and Aims: The composition of the Microbiota can be influenced by various lifestyle and environmental factors, including diet. We designed a study to investigate the improving effects of plant extract, the combination of turmeric, ginger, boswellia, and cat's claw on the abundance of key members of the gut microbiota, *Bacteroidetes*, *Akkermansia muciniphila (A. muciniphila), Faecalibacterium prausnitzii (F. prausnitzii), Firmicutes and Bifidobacterium* in mice treated with advanced glycation end products (AGE) rich high-fat diet (HFD).

Materials and Methods: Eighteen 2-month age male C57BL/6 mice were adopted to a regular diet for 1 week and then fed with an HFD or regular diet. After 8 weeks of diet, animals received plant extract concurrently with HFD for 8 weeks. Stools were taken, DNA of stool samples was extracted, and qPCR of 16s rDNA universal primers was performed. Then the effect of plant extract on dysbiosis induced by AGE-rich HFD was accessed.

Results: Our results revealed the frequencies of *Bacteroidetes* (p=0.001), *A. muciniphila* (p= 0.0005), *F. prausnitzii* (p<0.0001), and *Bifidobacterium* (p= 0.0008) were reduced, whereas the frequency of *Firmicute* was increased in the AGE-rich HFD group. A significant increase in the F/B ratio was observed in the HFD group than in the regular diet group (p= 0.0003). plant extract reduced the F/B ratio and improved gut microbiota homeostasis.

Conclusion: Plant extract restored gut microbiota patterns in HFD-treated mice. It seems more studies are required to prove the application of plant extracts for modulating the gut microbiota as a promising new biomarker with potential for therapeutic applications.

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Introduction

Advanced glycation end products (AGEs) are a heterogeneous class of products generated by non-enzymatic reactions between free amino acids/ lipids/ nucleic acids/ and α-dicarbonyl or sugars [1]. Aging can lead to the accumulation of endogenous AGEs and oxidative stress. Furthermore, the sources of exogenous AGEs, such as smoking and diet, considerably increase their amount in the body [2]. The nutritional composition (protein, fat, and carbohydrate) and conditions of cooking (high temperature, high pH, and long-time cooking) are the most important dietary factors determining AGEs [3]. A diet high in AGEs is closely related to some pathogenic mechanisms, including low-grade inflammation, dysfunction of endothelium, and oxidative stress, responsible for chronic disorder onsets such as diabetes, cardiovascular diseases, cancer, and renal disease [4, 5]. The intestinal microbiota may metabolize some dietary AGEs not defecated and absorbed. Afterward, the role of residual AGEs has attracted attention as a possible link to the composition of the gut microbiota. [4]. The microbiota of the gut is a very complex and dynamic ecosystem, and its homeostasis maintenance is important for the health of humans. Composition imbalances of the gut microbiota might damage the function of the gut barrier and increment the endotoxins level in the bloodstream leading to endotoxemia of metabolic [6]. Recent animal research has offered that diets enriched with AGEs are related to changes in intestinal microbiota composition, such as a reduction in the abundance of *Lactobacilli*, *Bacteroidetes*, and *Bifidobacteria* [7, 8]. Considering these proposes, the efficacy of gut microbiota can be improved following the usage of some dietary supplements, including herbal extracts, due to their active ingredients from plants which can change the level of beneficial bacteria and the production of the metabolites in the gut [9, 10]. The rhizome of Turmeric (*Curcuma longa*) is widely consumed as a dietary spice and coloring agent, particularly in Asia. Curcumin is the main active constituent of turmeric. It is a polyphenol component that has increasingly received attention for medical applications and pharmacological activities [11, 12]. Previous studies showed that the administration of curcumin may result in effects of regulative on the microbiota community [13]. Furthermore, the rhizome of ginger (*Zingiber officinale Roscoe*) has been commonly valued as a spice and an herbal remedy for a long time [14]. Various bioactive compounds have been known in ginger, such as terpene and phenolic compounds. Recently, ginger has attracted increasing attention owing to biological activities such as antioxidant, neuroprotective, anti-inflammatory, and antibacterial activities [15]. Additionally, the gum resin of *Boswellia* trees has been utilized for treating various infectious and inflammatory diseases in herbal medicine [16]. Among different constituent varieties of *Boswellia* species, Boswellic acids (pentacyclic triterpene acids) accounts for the pharmacologically active substances [17]. Also, scientific research into *Uncaria tomentosa* (cat's claw) extracts and constituents has revealed some therapeutic properties, such as

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immunomodulating, antioxidant, anti-inflammatory, antiviral, and anti-microbial activities [18]. The objectives of the current study were first to assess changes in gut microbiota by AGEs diet, then ameliorative effects of the Phyto Compound (Turmeric, ginger, *Boswellia*, and *Uncaria tomentosa*) against dysbiosis in mice.

Materials and Methods

Experimental design

Male C57BL/6 mice (2-month-old; 14±3 g) were purchased from the Royan Institute for Biotechnology (Isfahan, Iran), maintained under standard conditions: 45–55% humidity and 23–24 °C temperature, also a dark-light cycle of 12 hours, After one week of acclimation feeding, 18 mice were randomly divided to three groups: regular diet (ND) fed with pellet diets and water *ad libitum* (control group; n= 6), AGE-rich high-fat diet (HFD) (n= 6), AGE-rich HFD and plant extract (PE) 0.6 mg/g (HFD/PE; n= 6) 16 weeks. The Ethics Committee of the Royan Institute accepted all protocols of animal practice.

Preparation of PE

Phyto Arthrit, a combination of four plants powder: turmeric (31%), ginger (29.5%) and, Boswellia (29.5%), Uncaria tomentosa (10%) were prepared from Goldaro Pharmaceutical Company (Isfahan, Iran), was dissolved in distilled water and daily gavaged to mice for 8 weeks.

Fecal DNA extraction

Fecal samples were collected in the 17th week. Samples in the cold chain were immediately transferred to the laboratory for storage. These samples were kept at -80 °C upon arrival until further processing. Bacterial fecal DNA was isolated using the QIAamp DNA Stool Mini Kit (Qiagen Retsch GmbH, Hannover, Germany) according to the manufacturer's protocol. The integrity and length of the extracted bacterial DNA of samples have assessed the usage of gel electrophoresis (Fig. 1), and concentration and purity were determined using a Nanodrop spectrophotometer (Thermo Scientific, USA). The extracted overall DNA turned into saved at -20 °C.

quantitative polymerase chain reaction (qPCR) analyses of 16S rDNA

Bacterial abundance was analyzed using SYBER green qPCR (Light Cycler® 96 SW 1.1; Roche, Germany) [19, 20]. Each qPCR reaction consisted of the DNA template (1 µl), SYBR Premix Ex Taq II (Takara, Japan), and 0.5 µl of specific16s rDNA primers (Table 1) for each bacterium and was conducted in triplicate. The amplification program was run as follows: 95 °C for 60 seconds (1 cycle), followed by denaturation at 95 °C for 5 seconds (40 cycles), annealing at 55 °C for 30 seconds, and extension at 72 °C for 30 seconds. Then, melting curve analysis was performed to control the specificity of the PCR reaction, followed by 1 cycle at 94 °C for 5 seconds, 60 °C for 60 seconds, and 94 °C for 1 second (Fig. 2). Each sample's threshold cycle (ct) is registered by the thermocycler.

Standard curve

A standard curve was generated using serial dilutions of DNA from a standard strain of *Escherichia coli* that was used to calculate the DNA concentration of each bacterium from stool samples. The standard curve is a semi-log regression line plot of computerized tomography

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versus log DNA concentration. Then the number of template copies was determined by using the online formula in (cels.uri.edu/gsc/cndna.html).

Statistical analysis

GraphPad Prism Software (Version 9.0 Graph Pad Software Inc., USA) was used to determine mean differences between the groups. Data were triplicate data sets for each sample and were analyzed by One-way analysis of variance (ANOVA). $p < 0.05$ was considered statistically significant.

Results

PE improved the gut microbiota in AGE-rich HFD

Compared with the control group, HFD treatment decreased the relative abundance of *Bacteroidetes* ($p = 0.001$), *Bifidobacterium* ($p = 0.0008$), *A. muciniphila* ($p = 0.0005$), and *F. prausnitzii* ($p < 0.0001$), and increased the relative abundance of *Firmicutes*. In contrast, PE treatment improved their relative abundance of them (Fig. 3).

F/B ratio

Our results showed that the abundances of *Firmicutes* and *Bacteroidetes* were significantly increased in the AGE-rich HFD group and decreased in the AGE-rich HFD/PE group. Besides, the F/B ratio was significantly higher in the AGE-rich HFD ($p = 0.0003$) than in the control group (Fig. 3).

Table 1. 16S rRNA gene-specific primers for the studied bacterial group/species

Primers	Sequence (5′–3′)	Amplicon size (bp)	Reference
Firmicutes	TGAAACTYAAGGAATTGACG ACCATGCACCTGTC	155	[45]
Bacteroidetes	CTGAACCAGCCAAGTAGCG CCGCAAACTTTCACAACTGACTTA	230	[46]
Bifidobacterium	TCGCGTCYGGTGTGAAAG CCACATCCAGCRTCCAC	128	[46]
Akkermansia muciniphila	CAGCACGTGAAGGTGGGGAC CCTTGCGGTTGGCTTCAGAT	327	[46]
Faecalibacterium prausnitzii	GGAGGAAGAAGGTCTTCGG AATTCCGCCTACCTCTGCACT	248	[46]
Escherichia coli	CATTGACGTTACCCGCAGAAGAAGC CTCTACGAGACTCAAGCTTGC	195	[46]

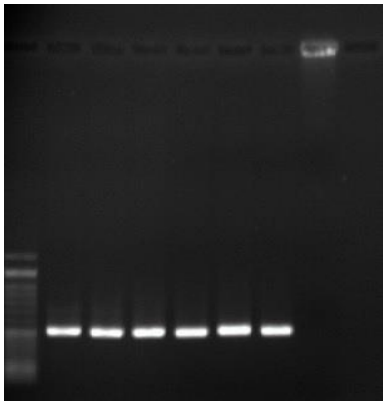

Fig. 1. Stool DNA extracted from samples

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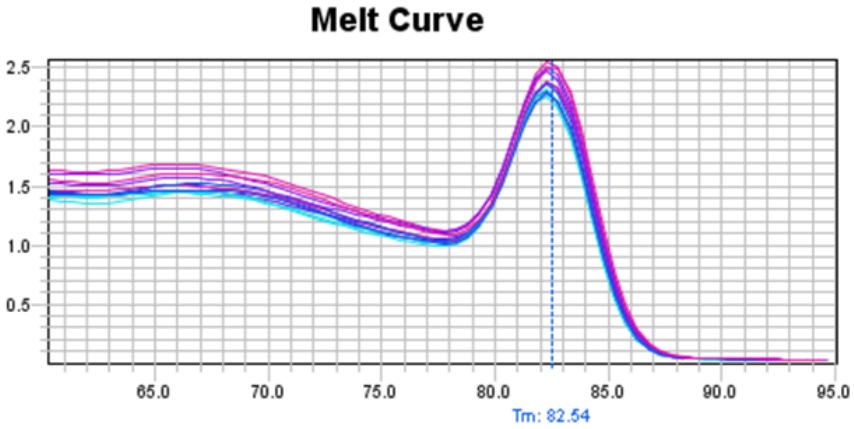

Fig. 2. Melt curve from qPCR of the 16srDNA gene

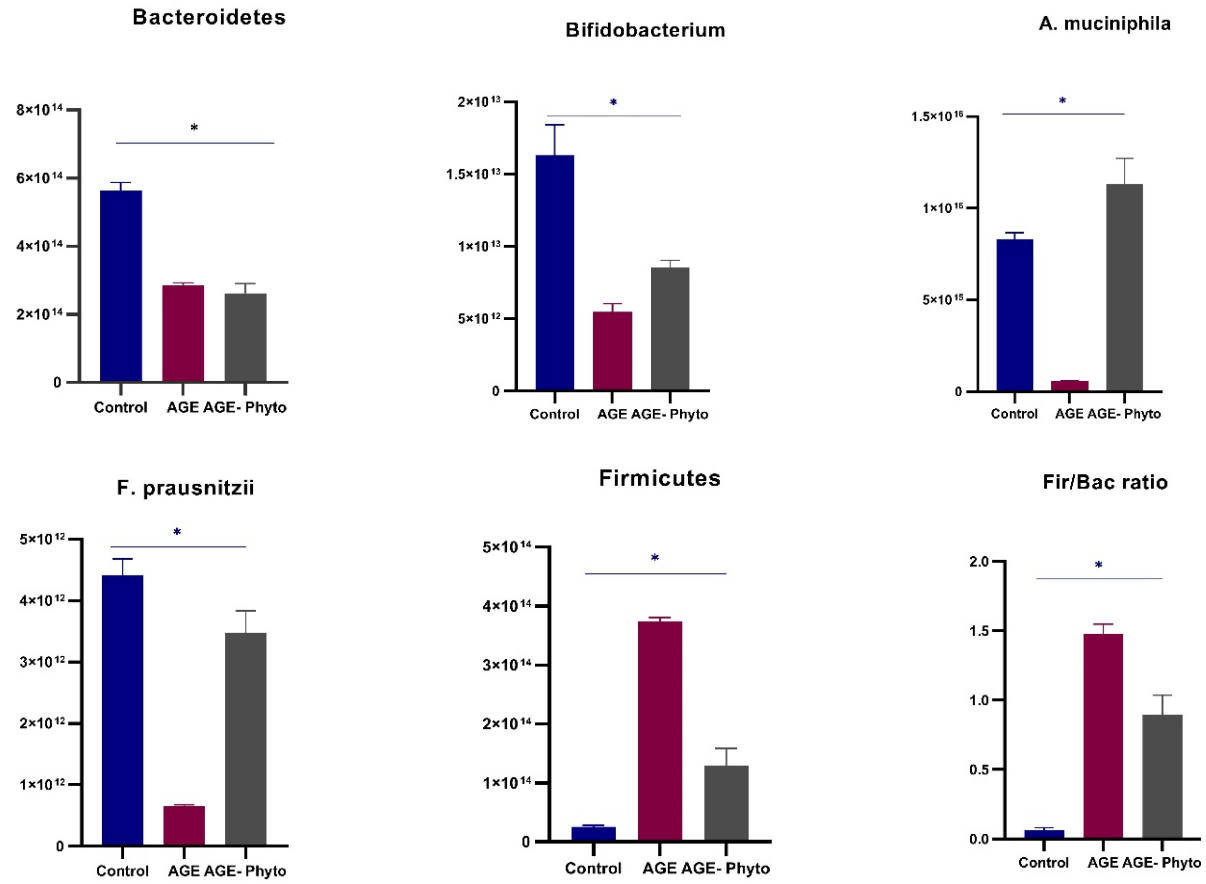

Fig. 3. The abundance of vital microbiota in each group. AGEs= Advanced glycation end products; AGE/Phto= AGEs/ Phyto extracts. *p < 0.05

Discussion

There is increasing evidence that the microbiota plays a key role in maintaining host health. Accordingly, any perturbations in gut microbiota composition, such as the decrease in diversity and prevalence of bacteria, can cause the progression of many human diseases, such as inflammatory bowel disease, obesity, diabetes, asthma, allergies, neuro-

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inflammation, and depression [21-24]. The composition of Microbiota can be influenced by various environmental and lifestyle factors, including diet, which significantly impacts gut microbiota diversity [23, 25, 26]. A large body of evidence revealed that the modern lifestyle with AGEs rich western diet by perturbations in the microbiota composition of the gut and reducing bacterial diversity (dysbiosis), provides a basis for the dysfunction of the immune system, then causes altered intestinal permeability and low-grade systemic inflammation [3, 27, 28]. This experiment aimed to investigate the relationship between the consumption of AGE-rich HFD and intestinal microbiota and then assess the effects of PE on gut dysbiosis induced by HFD. For this purpose, mice were first subject to AGE for a long time (16 weeks); at the same time, PE was gavage to mice in the eighth week. Our results demonstrated that the F/B ratio in the HFD group significant increase than to the ND group. The abundance of *Bifidobacterium*, *Bacteroidetes*, *A. muciniphila* and, *F. prausnitzii* was significantly decreased, whereas the frequency of *Firmicute* was significantly increased in the AGE-rich HFD group. In comparison, PE reduced her F/B ratio and improved gut microbiota homeostasis. In line with our study, Wang et al. reported that treatment of mice with high-AGE diets leads to reduced diversities of the gut microbiota. They also showed that the abundance of butyrate-producing bacteria such as *Lachnospiraceae*, *Bacteroidales*, and *Ruminococcaceae* decreased after an AGE-rich diet [4]. Loss of butyrate-producing bacteria has been speculated to lead to intestinal epithelial barrier dysfunction, immune stimulation, and low-grade systemic inflammation [5, 29]. Also, Hassan et al., in agreement with our results, reported that long-term HFD in mice decreased the relative prevalence of *Bacteroidetes*. Likewise, the *Firmicutes* to *Bacteroidetes* ratio, as found in obese mice and humans, was increased in response to HFD [30]. Seiquer et al. showed that the possible effects of the AGEs diet on the composition of gut bacteria depend on the amount and chemical structure of the different compounds [31]. Recent experiments have provided direct and indirect evidence that isolated compounds of plant extracts are potent modulators of gut microbiota composition [32, 33]. The plant extract used in this study comprises turmeric, Boswellia, ginger, and cat's claw which have already been testified for different biological functions, such as antibacterial, anti-inflammatory, antioxidant, antitumor, and neuroprotective [34-37]. Previous studies show curcumin exerts direct regulatory effects on the intestinal microbiota [21]. Curcumin can alter the ratio of beneficial to harmful bacteria in the intestinal microbiota community in favor of beneficial bacteria such as butyrate-producing bacteria, *bifidobacterial,* and *lactobacilli*. It also decreases the abundance of pathogenic bacteria such as *Prevoellaceae, Coriobacterales, Rikenellaceae*, and *Enterobacteria*, commonly associated with developing systemic diseases [38-41]. Shen et al. demonstrated that oral curcumin administration in C57BL/6 mice significantly altered the

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abundance of several pathogenic families, such as *Bacteroidaceae*, *Prevotellaceae*, and *Rikenellaceae* [39]. Wang et al. revealed that ginger treatment in HFD-fed mice modulates the intestinal microbiota composition and increases species of *bifidobacteria* and SCFA-producing bacteria (*Alloprevotella* and *Allobaculum*). [42]. Suther et al. observed that the administration of Boswellia serrata to mice for 14 days showed a significant reduction in the number of gut bacteria in male mice, with no effect in female mice [43].

Conclusion

In the present study, HFD altered gut microbiota composition in mice treated with AGE-rich HFD compared to control, while consumption of the PE compound could ameliorate gut dysbiosis. Modulation of the gut microbiota by dietary interventions such as plant extracts as modifiable targets has increased in recent years, both in research interest and product development. However, it seems more studies are required to prove the application of plant extract for modulating the gut microbiota as a promising new biomarker with potential for therapeutic applications.

Conflict of Interest

The authors declare that they have no competing interests.

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