Tropical Journal of Pharmaceutical Research January 2024; 23 (1): 141-146
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v23i1.18

Original Research Article

Effect of berberine on glucolipid metabolism, carotid thickness, vascular endothelial function, oxidative stress and intestinal flora in patients with coronary heart disease

Fengming Yang*, Chuiyi Zeng, Zhenyi Chen
Department of Cardiology, Henan Provincial Hospital of Traditional Chinese Medicine, The Second Hospital Affiliated to Henan University of Chinese Medicine, Zhengzhou City, Henan Province 450002, China

For correspondence:* ***Email:* *yfming1220@outlook.com*

Sent for review: 29 June 2022 *Revised accepted: 3 January 2024*

Abstract

Purpose: *To investigate the effect of berberine on glucolipid metabolism, carotid thickness, vascular endothelial function, oxidative stress and intestinal flora in coronary heart disease (CHD) patients.*
Methods: *68 patients with CHD admitted to the Department of Cardiology, Henan Provincial Hospital of Traditional Chinese Medicine, China were assigned to two groups of 34 patients each. Control group received anti-CHD treatment while study group was given 0.3 g of berberine three times daily for 4 weeks. Changes in glucolipid metabolism, carotid thickness, vascular endothelial function, oxidative stress and intestinal flora were assessed.*
Results: *Total cholesterol, triglyceride, tumor necrosis factor-α, interleukin (IL)-2 and IL-1β of CHD patients from study group were significantly decreased compared to control group ($p < 0.05$) while superoxide dismutase ($p = 0.019$) and total antioxidant capacity ($p = 0.009$) of CHD patients in study group were significantly increased. In addition, reduced endothelin-1 and elevated Nitric Oxide levels were shown in CHD patients in study group ($p < 0.001$). Furthermore, the carotid intima-media thickness decreased in study group, while Aquificae, Paraprevotella, Abiotrophia, Rubrobacterales, Bacteroidales and other microbes were abundant in the intestinal tract of study group patients.*
Conclusion: *Berberine improves glucolipid metabolism, carotid thickness, vascular endothelial function, oxidative stress and intestinal flora in CHD patients. Berberine may therefore be effective in the treatment of CHD. Further studies are, however, required to establish these claims.*

Keywords: *Berberine, Coronary heart disease, Glucolipid metabolism, Carotid thickness, Vascular endothelial function, Intestinal flora*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

As with most complex illnesses, the risk of suffering coronary heart disease (CHD) is influenced by a combination of genetics, lifestyle and other factors [1]. Despite crucial advances in the field of epidemiology and translational research in strengthening understanding of the pathophysiology of CHD, the disease continues to be a principal cause of worldwide fatalities [2]. For example, over 900,000 people in the United States have heart attacks or die from CHD each

year. The occurrence of this disease is closely associated with the patient's blood lipid levels. It is exacerbated by an unhealthy lifestyle and diet, leading to a significant increase in the incidence of CHD [3]. Besides, the increase in age, environmental pollution, alcohol and tobacco intake also enhances the occurrence of CHD. The treatment of the disease is mainly through drugs, supplemented by the optimization of diets [4]. Among them, traditional Western drugs against myocardial ischemia and platelet aggregation cannot be applied to treat this disease without certain side effects completely. Therefore, more suitable and effective drugs should be explored for effective treatment of CHD [5]. The latest genetic tests can enable accurate medical treatment by identifying subgroups of patients with an elevated risk of CHD or distinct underlying pathophysiological factors. In recent times, proprietary Chinese medicines have become popular for the treatment of many diseases [6-8]. Berberine, a kind of quaternary ammonium salt extracted from *Coptis chinensis,* consists of the isoquinoline alkaloid, proberberine, which possesses anti-arrhythmia and antihypertensive functions [9]. Nevertheless, the specific function of berberine in CHD treatment has not been clarified. Therefore, this investigation was done to evaluate the therapeutic influence of berberine on CHD via comparison of the changes of various indices in patients with and without CHD, who were treated with berberine. This study will provide insights into potential follow-up studies in treatment mechanisms.

METHODS

Subjects

Sixty-eight (68) CHD patients were enrolled in this study and were followed up for nearly one year. The study was approved by the Ethics Committee of Henan Provincial Hospital of Traditional Chinese Medicine (approval no. 20171105HN). Signed, written informed consent forms were obtained from the patients and/or guardians. All procedures were conducted in compliance with the ethical standards of the Institutional Review Board and the Declaration of Helsinki [10]. Patients were evenly divided into two groups, the control and study groups, with 34 patients in each group. The mean age of control group and study group patients were 61.51 ± 3.58 years and 63.83 ± 5.32 years, respectively. Coronary angiography was performed in both groups and patients who were allergic to berberine or opposed to participating in the study treatment were excluded.

Treatments

Patients in the control group received routine anticoagulation, anti-myocardial ischemia, and other coronary heart disease treatment regimens. In study group, in addition to the same routine treatment, patients were also treated with 0.3 g of berberine, taken three times a day after meals, with each course of treatment lasting for 4 weeks.

Determination of intestinal flora

Fresh fecal samples weighing 3 to 5 g were collected from CHD patients in both the control and study groups. These samples were subsequently frozen and stored in liquid nitrogen tanks. After collecting samples from all patients, bacterial flora DNA was extracted using a fecal bacteria DNA extraction kit and the analysis of flora composition was conducted through sequencing after amplification.

Assessment of inflammatory and oxidative stress indices

Determination of inflammation and oxidative stress indices, including interleukin (IL)-2, IL-1β, tumor necrosis factor-α (TNF-α), superoxide dismutase (SOD), malondialdehyde (MDA) and total antioxidant capacity (T-AOC), were done using enzyme-linked immunosorbent assay kits. The patient's sera were tested using the R&D kit according to the operation manual. The absorbance of each well was read after sampling and incubation.

Evaluation of glucolipid metabolism

Fresh sera were sent to the clinical laboratory and the determination of glucolipid metabolism indicators was performed using a biochemical analyzer. All testing procedures were conducted by senior laboratory physicians and the equipment underwent routine quality control.

Endothelial function test in vessels

Endothelin-1 (ET-1), nitric oxide (NO) and intercellular adhesion molecule-1 (ICAM-1) were evaluated through assay kits following operational instructions of each kit.

Carotid thickness

Carotid intima-media thickness (IMT) was measured via two-dimensional ultrasonography with Doppler ultrasonography for research objects.

Statistical analysis

Data analyses were done using SPSS 23.0 software. Group comparison was carried out *t*-test. $P < 0.05$ was set as statistically significant.

RESULTS

Glucolipid metabolism

As shown in Table 1, CHD patients in study group exhibited a significant reduction in total cholesterol (TC; $p = 0.043$) and triglyceride (TG; $p = 0.042$) compared to control group.

Inflammatory factors

Results in Table 2 show that there was a significant decrease in the TNF-α ($p < 0.001$), IL-2 ($p < 0.001$) and IL-1β ($p = 0.024$) levels in patients in study group when compared to the control group (Table 2).

Oxidative stress indices (SOD, T-AOC and MDA)

As depicted in Table 3, CHD patients in study group exhibited increased SOD ($p = 0.019$) and T-AOC ($p = 0.009$) levels compared to control group.

Vascular endothelial function (ET-1, NO and ICAM-1)

As indicated in Table 4, ET-1 was significantly downregulated in study group ($p < 0.001$) while the content of NO was upregulated ($P < 0.001$) in study group compared to the control group.

Table 1: Differences in glucolipid metabolism between groups

Parameter	Control	Study	*t*	*P*-value
Fasting blood glucose (mmol/L)	4.75±0.87	4.82±1.03	2.84	0.428
Triglyceride (mmol/L)	2.74±0.21	2.48±0.23	6.98	0.042
Glycosylated hemoglobin (%)	6.10±0.70	6.0±0.50	4.27	0.104
Total cholesterol (mmol/L)	6.22±0.42	5.82±0.28	6.84	0.043
Low-density lipoprotein (mmol/L)	4.32±0.58	4.08±0.47	2.64	0.435

Table 2: Inflammatory factors in study group compared with the control group

Parameter	IL-2 (ng/L)	IL-1β (ng/L)	TNF-α
Control	18.42±1.52	14.39±1.15	23.24±2.65
Study	14.74±1.38	12.64±1.02	17.34±1.48
T	11.25	8.35	12.31
P-value	0.000	0.024	0.000

Table 3: Oxidative stress indices of CHD patients in both groups

Parameter	SOD (U/mL)	T-AOC (U/mL)	MDA (nmol/mL)
Control	62.52±7.46	7.49±0.79	7.25±0.76
Study	88.49±9.61	9.27±0.95	7.11±0.84
t	8.94	10.53	3.64
P-value	0.019	0.009	0.214

Table 4: Differences in vascular endothelial function in both groups

Parameter	ET-1 (ng/L)	NO (μmol/L)	ICAM-1 (μg/L)
Control	48.35±4.98	33.47±4.38	237.15±26.14
Study	39.15±3.65	57.58±6.45	242.84±25.64
t	13.25	14.85	3.98
P-value	0.000	0.000	0.129

Intima-media thickness (IMT)

The carotid intima-media thickness (IMT) was significantly decreased in study group (p = 0.021) compared to the control (Figure 1).

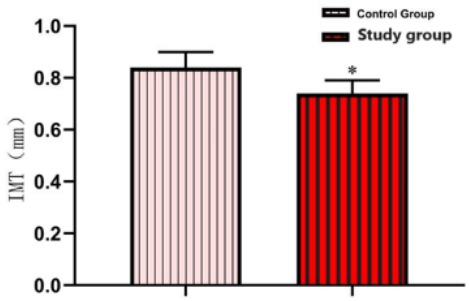

Figure 1: The carotid intima-media thickness (IMT) levels of patients in both groups (*p < 0.05)

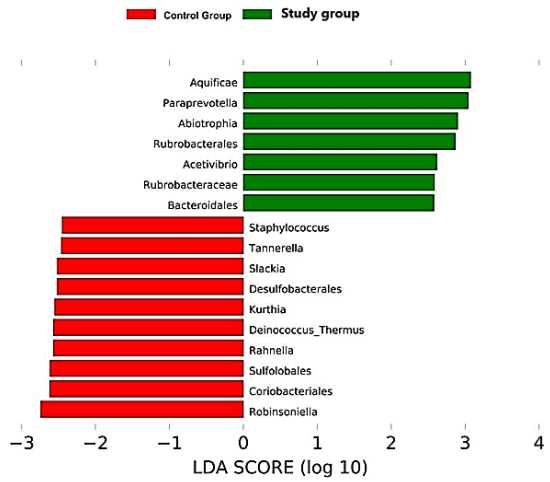

Figure 2: Linear Discriminant Analysis (LDA) score of intestinal flora in the control and study group

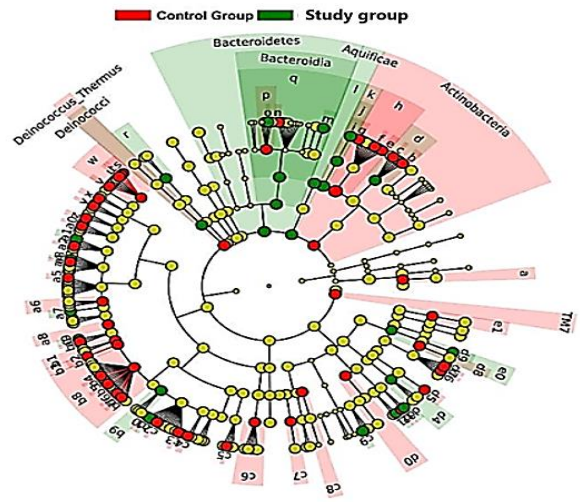

Figure 3: Linear discriminant analysis Effect size (LEfSe) analysis of intestinal microflora

Intestinal microflora

The intestinal tract of CHD patients in study group had an abundance of intestinal microorganisms such as *Aquificae*, *Paraprevotella*, *Abiotrophia*, *Rubrobacterales* and *Bacteroidales* while the presence of *Robinsoniella*, *Coriobacteriales*, *Sulfolobales*, *Rahnella*, *Desulfobacterales* and other microorganisms were decreased (Figure 2 and 3).

DISCUSSION

The basic pathological manifestations of CHD are vascular and myocardial dysfunction, stimulated and aggravated via ischemia, hypoxia, oxidative stress, inflammation and apoptosis. Due to the larger population of CHD patients, the search for effective drugs to cure CHD is a hot research topic [11]. Clinical requirements can no longer be met via traditional Western medicine on account of its disadvantages like severe side effects and relatively limited therapeutic effect [12]. The application of traditional Chinese medicines, e.g. berberine, may take on a particular effect on CHD therapy [13,14]. Recently, berberine has become a valid substitute for the treatment of dyslipidemia-linked diseases, can mitigate the lipid profile and may regulate lipids in CHD patients [15].

In humans, the multiple influences of berberine have been confirmed in quantity randomized clinical trials. Furthermore, initial clinical evidence confirms that berberine alleviates endothelial inflammation and promotes vascular health in patients who have been diagnosed with cardiovascular disease [16]. Overall, the available evidence indicates that berberine might be applied in chronic cardiometabolic disease therapy. However, the specific mechanism of its effect on CHD has not been fully elucidated. The gut microbiome is also influenced by dietary patterns, drug types and doses. Variations in the constituent and abundance of intestinal flora are influential in the systemic inflammation and immunity of some people, partly accelerating the progression of diseases [17,18]. A previous study revealed alterations in the configuration and metabolic activity of intestinal microbiota in CHD patients, with an augmentation in bacteroides and protein bacteriophyta, as well as a decrease in Firmicutes and Fusobacteria [19]. The ratio of trimethylamine to trimethylamine nitrogen oxide, a metabolite of intestinal bacteria, is also implicated in CHD. In this study, it was demonstrated that *Aquificae*, *Paraprevotella*, *Abiotrophia*, *Rubrobacterales*, *Bacteroidales* and other microbes were abundant in the intestinal

tract of patients with CHD in study group. In contrast, *Robinsoniella*, *Coriobacteriales*, *Sulfolobales*, *Rahnella*, *Desulfobacterales* and other microorganisms were abundant in the intestines of patients with CHD in the control group. These results affirmed that the configuration and abundance of the intestinal microflora in CHD patients were distinctly changed after berberine treatment. This may influence the development and treatment of the disease. This result implies that the combination of certain microbiota inhibitors with berberine may offer better treatment for the disease in the future. In addition, comparison of the changes of various indices in CHD patients after berberine treatment showed that the levels of ET-1 in study group were reduced, while the NO levels were elevated. In addition, the total cholesterol, triglycerides and inflammation indices of CHD patients in study group were reduced versus control group. Furthermore, SOD and T-AOC of CHD patients from study group were increased compared to the control group while the IMT of study group was reduced versus the control. These results suggest that after berberine treatment, all the physical indicators of patients with CHD were alleviated. This may represent the mechanism of action of the drug in the treatment of CHD. However, further studies are required to elucidate the precise mechanism of the drug in the treatment of CHD patients.

Limitations of this study

In this study, a relatively small sample size of CHD patients was used which may impact the reliability of the conclusion. In future studies, the sample size will be increased.

CONCLUSION

Berberine mitigates glucolipid metabolism, carotid thickness, vascular endothelial function and oxidative stress in patients with CHD. In addition, berberine impacts the composition of patients' intestinal flora, leading to an increase in its diversity and suppression of disease progression. Berberine may therefore be effective in the treatment of CHD. Findings from this study offer a good direction for further studies.

DECLARATIONS

Acknowledgements

This work was supported by the Henan Province Special Project of Traditional Chinese Medicine Scientific Research (no. 2019JDZX003).

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Fengming Yang conceived and designed the study and drafted the manuscript. Fengming Yang and Chuiyi Zeng collected, analyzed and interpreted the experimental data. Chuiyi Zeng and Zhenyi Chen revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

REFERENCES

1. *Shao J, Chen W. Mitigating effect of clopidogrel and systematic management on adverse events after interventional therapy for coronary heart disease. Trop J Pharm Res 2022; 21(2): 387-392.*
2. *Zhang Z, Feng Q, Zhang M. Research progress and clinical Study on the correlation of vascular endothelial function and coronary heart disease or diabetes mellitus. Electronic J Cardiovas Dis Integ Trad Chin Western Med 2015; 3(06): 186-187.*
3. *Kivimäki M, Jokela M, Nyberg ST, Singh-Manoux A, Fransson EI, Alfredsson L, Bjorner JB, Borritz M, Burr H,*

Casini A, et al. Long working hours and risk of coronary heart disease and stroke: A systematic review and meta-analysis of published and unpublished data for 603,838 individuals. Lancet 2015; 386(10005): 1739-46.

4. *Houston M, Minich D, Sinatra ST, Kahn JK, Guarneri M. Recent science and clinical application of nutrition to coronary heart disease. J Am Coll Nutr 2018; 37(3): 169-187.*
5. *Wu L. Research progress in the treatment of coronary heart disease. Massage and rehabilitation medicine 2016; 7(11): 8-9.*
6. *Wei J, Zhu M, Yu R, Hao X, Qiao L, Ma T. Research progress of traditional Chinese medicine on coronary heart disease. Trad Chin Med Res 2020; 33(10): 74-77.*
7. *Zheng J, Li J. Clinical research progress of salvianolic acid for injection in the treatment of coronary heart disease angina pectoris. Drug Evaluation Study 2020; 43(09): 1919-1922.*
8. *Wang Z, Zhang R. Research progress of traditional Chinese medicine external treatment for coronary heart disease. The light of traditional Chinese medicine. Guangming J Chin Med 2020; 35(16): 2603-2605.*
9. *Ma G, Liu D. Pharmacological research progress of Coptis chinensis. Gansu Agriculture 2019; (10): 97-99.*
10. *World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA 2013; 310(20): 2191-2194.*
11. *He X, Liu M. Prevention and treatment strategies of coronary heart disease in China. Chin Gen Pract 2015; 18(02): 239-240.*
12. *Guidelines for rational drug use of coronary heart disease (2nd edition). Chin J Frontiers Med Sci (Electronic Version) 2018; 10(06): 1-130.*
13. *Cao X, Zhu N. Effect of berberine on myocardial apoptosis in rats with coronary heart disease and its mechanism. Chin J Integrat Med Cardio-Cerebrovas Dis 2019; 17(22): 3504-3507.*
14. *Yang R, Yin J. Effects of berberine combined with rosuvastatin calcium on blood lipid, serum inflammatory factors and endothelial function in patients with coronary heart disease. J Modern Med Health 2019; 35(03): 431-433.*
15. *Zhuang W. Protective mechanism of berberine on human coronary artery endothelial cell injury induced by fluctuating high glucose. Nanjing University of Traditional Chinese Medicine 2019; Vol. Doctor, 80.*
16. *Deng X, Xie N. Research progress in the pharmacodynamics of berberine and its derivatives. Acta Chin Med Pharmacol 2017; 45(04): 108-111.*
17. *Kåhrström CT, Pariente N, Weiss U. Intestinal microbiota in health and disease. Nature 2016; 535(7610): 47.*
18. *Sittipo P, Lobionda S, Lee YK, Maynard CL. Intestinal microbiota and the immune system in metabolic diseases. J Microbiol 2018; 56(3): 154-162.*
19. *Liu L, He X, Feng Y. Coronary heart disease and intestinal microbiota. Coron Artery Dis 2019; 30(5): 384-389.*