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Nitric Oxide（NO）is a Driving Force for Unobstructed Qi−blood Circulation*

ZHAO Bao-Lu**
(*Institute of Biophysics, Chinese Academy of Sciences, Beijing* 100101, China)

Abstract We review nitric oxide (NO) free radical as adriving force for Qi-blood circulation; antioxidants' scavenging oxygen free radicals, protecting NO and helping NO to drive Qi-blood circulation, as well as their protecting cardiovascular and cerebrovascular health together with NO. NO and natural antioxidants can improve the longevity, and synergistically eliminate the damage caused by inflammation.Traditional Chinese medicines (TCM) including natural antioxidants ensure health *via* activating Qi-blood circulation and removing blood stasis, in which NO plays an important role in the invigoration of Qi-blood circulation.

Key words nitric oxide, oxygen free radicals, natural antioxidants, traditional Chinese medicine
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It is well known that "if circulation of Qi-blood is free (unobstructed, patency), there is no pain, otherwise there is a pain", in Chinese tradition medicine theory. The functions of organs are normal and the body is health only in the condition of Qi-blood circulation is free. Otherwise, if the Qi-blood was blocked up, there would be myocardial infarction, stroke, inflammation, pains and other diseases. What is the driving force for free Qi-blood circulation? It is discussed in this paper.

1 Nitric oxide free radical is a driving force for free Qi−blood circulation

1.1 NO is endothelium−derived relaxing factor（EDRF）

Three American scientists have found that NO is endothelium-derived relaxing factor (EDRF), as a major signaling molecule in the cardiovascular, immune and nervous systems, can promote blood vessel dilatation and blood circulation. They shared the Nobel Prizein Physiology and Medicine in 1998[1-3].

Nitric oxide is a simple gas in blood vessel generated by endothelium from L-arginine through catalytic reaction of NO synthase existed in a great variety of cell types. NO entranced into smooth muscle and combined with Fe^{2+} on the group of haemoglobin in soluble guanylyl catalase (sGC), activated soluble guanylyl (sG) and guanosine monophosphate (GM), promoted the level of cyclic guanosine monophosphate (cGM) and activated cGM protein kinases. Then the phosphorylation of troponin and K^+ pathway on muscle cells membrane were promoted, the affinity of troponin C for Ca^{2+} and K^+ pathway on muscle cells membrane was decreased, leading to expansion of blood vessels, decrease of vasodilation and arterial pressure and free of Qi-blood flow and prevented platelet aggregation[4-5].

As a signal, NO plays a variety of functions in the body through multiple pathways. For example, NO is involved in many activities, such as regulating blood pressure, immune response, neuron plastic, learning and memory *etc*. At the same time, NO is closely related to a variety of diseases, such as heart disease, stroke, Alzheimer's disease, Parkinson's disease, diabetes, sexual dysfunction and aging *etc*[6-8].

1.2 Microcirculation is the basic for Qi−blood circulation and exchange of materials and energy

Microcirculation is the basic for Qi-blood circulation and exchange of materials and energy

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** Corresponding author.
Tel：86-13681023252，E-mail：zhaobl@sun5.ibp.ac.cn
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(Figure 1). The essence from digested food in digestive tracts (ague, stomach) and oxygen from lung enter artery blood vascular and capillary and support the nutrition and oxygen for the cells and tissues, then the carbon dioxide and trash from metabolism enter venin vascular and remove out of body. Keeping this Qi-blood circulation free and balance of oxygen and nutrition is a key factor for the health. If it was blocked, the tissues will be ischemia and hypoxia, and the cells will be death and it will be difficulty to keep normal functions for all organs of the body. All diseases and even aging connect with it. It is a time bomb in the body. Basic forms of metabolism of body is transportation of oxygen and nutrition and removal of carbon dioxide and waste through Qi-blood microcirculation. It is the premise to maintain self-healing power and self-vitality.

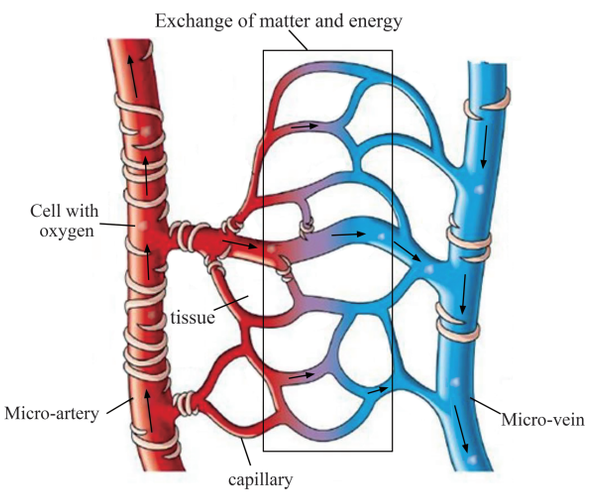


Fig. 1 Microcirculation is the basic for free of Qi−blood circulation and exchange of substance and energy

The blocking degree of Qi-blood microcirculation reflects cell death and aging levels of body, so aging and diseases are reflections of body's Qi-blood microcirculatory disturbance. NO free radicals can improve Qi-blood microcirculation, delay aging and prevent various diseases such as diabetes, hypertension, cancer *etc*.

NO free radicals play an important role in learning and memory processes. First of all, NO is generated in the synaptosome and retrogradely diffused to the presynaptosome, where cGMP synthase is activated and a large number of cGMP is synthesized. It maintains the long-term potentiation (LTP) of hippocampal synapses. This is another important progress following the discovery of N-methyl-D-aspartate (NMDA) receptors[9]. The study of the relationship between NO and synaptosome modulation in learning and memory will show new prospects for the principle of brain information processing. If Qi-blood microcirculation disorders occur in brain, a series of brain disorders will occur, such as insomnia and amnesia, dizziness and headache, failing memory, myopia and presbyopia, premature gray hair in less serious cases and dementia, Parkinson, stoke, brain atrophy in serious disorders.

If Qi-blood microcirculation disorders occur in the heart, a series of heart disorders will occur, such as chest tightness and chest pain, palpitation, arrhythmia, hypotension, anginapectoris, myocardial infarction[10].

If Qi-blood microcirculation disorders occur in liver, a series of liver disorders will occur, such as, hepatitis A, B and C, fatty liver and cirrhosis and even liver cancer[11]. NO free radical can relax blood vessels and free Qi-blood microcirculation. Such series of symptoms in heart and liver disorders will not appear.

We studied the protective effect of NO free radical on cardiac ischemic injury and it was found that the arrhythmias decrease with the concentration of L-arginine (Table 1)[12].

Table 1 Influence of L−arginine−NO on the ventricular arrhythmias in myocardial ischemia−reperfusion injury *in vivo* ($\bar{x}\pm s$, n=6−16)

Group	BG	TG	VP	VF	VT	TAR/%
N	0/9	0/9	0/9	0/9	0/9	0
I	0/10	0/10	0/10	0/10	0/10	10
IR	0/16	0/16	3/16	3/16	1/16	43.75
IR+LA						
5	0/6	0/6	1/6	0/6	0/6	16.67
50	0/8	0/8	1/8	1/8	0/8	2 500
100	0/6	0/6	0/6	0/6	0/6	0.00
500	0/9	1/9	1/9	1/9	0/9	33.33

BG: Bigeminy; TG: Trigemini; VP: Ventricular premature; VF: Ventricular fibrillation; VT: Ventricular tachycardia; TAR: Total arrhythmias rate; N: Normal control heart; I: Ischemia; IR: ischemia reperfusion; LA: L-arginine (5, 50, 100, 500 mg/kg, i.p.).

If Qi-blood microcirculation disorder occurs in the immune system, a series of symptoms of immune system disorders occur, such as diseases in lymphatic and blood systems, tonsillitis and liver[13].

Macrophages produce NO free radicals can kill invasive microorganisms and tumor cells during phagocytosis and stimulation.

If microcirculation occurs in the reproductive system, a series of reproductive disorders may occur, such as premature ejaculation, impotence, low sexual function and prostatitis for men and menstrual disorder, infertility, ovarian and uterine problems for women[14]. An oral drug for erectile dysfunction and premature ejaculation can significantly improve the symptoms, which can help couples to have a satisfying sex life. Studies have shown that after taking Viagra, vascular smooth muscle of the penile cavernous body relaxes under the action of NO produced by the drugs, blood flow increases, cavernous body congestion, penile erection, which has a therapeutic effect on penile erectile dysfunction. Clinical trials showed that about 78% of the Europeans and Americans took sildenafil and its effect increased with the increase of drug concentration in the blood[15].

1.2 Targeted delivery of nitric oxide *via* a "bump−and−hole"−based enzyme−prodrug pair

If there is Qi-blood clogging in the limbs, there will be a series of symptoms such as numbness of waist and leg, pain and so on. The spatiotemporal generation of NO, a versatile endogenous messenger, is precisely controlled. Hou *et al*. [16] developed a novel NO delivery system *via* modification of an enzyme-prodrug pair of galactosidase-galactosyl-NONOate using a "bump-and-hole" strategy. Precise delivery to targeted tissues was clearly demonstrated by an *in vivo* near-infrared imaging assay. The therapeutic potential was evaluated in both rat hind limb ischemia and mouse acute kidney injury models. Targeted delivery of NO clearly enhanced its therapeutic efficacy in tissue repair and function recovery and abolished side effects due to the systemic release of NO. The developed protocol holds broad applicability in the targeted delivery of important gaseous signaling molecules and offers a potent tool for the investigation of relevant molecular mechanisms[16].

2 Natural antioxidants protect NO free radicals and exert the driving force of Qi−blood patency

As mentioned above, as a signal, NO plays a variety of functions in the body through multiple pathways. But if there are more NO in the ischemia-reperfusion heart, it will lead to more ventricular arrhythmias (Table 1). Reactive oxygen species (ROS), such as superoxide, hydroxyl and NO radicalswill react each other to form peroxynitrite ($ONOO^-$), and triggers apoptotic cellular death process[17-19] (Figure 2). Oxidative stress can damage cells, leading to hyperlipidemia, hyperglycemia and hypertension, heart disease and brain disease. Antioxidants may prevent apoptosis by means of scavenging ROS and $ONOO^-$ [20-22].

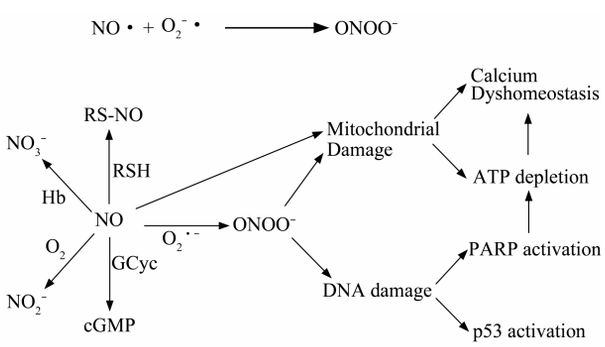


Fig. 2 Superoxide and NO radicals will react each other to form peroxynitrite ($ONOO^-$), and triggers apoptotic cellular death process

2.1 Natural antioxidants protect NO to play the driving force of Qi and blood patency

We found that natural antioxidants can protect NO, promote NO production, promote cardiovascular and cerebrovascular health together with NO free radicals. Natural antioxidants can effectively scavenge oxygen free radicals, maintain the balance of free radical metabolism *in vivo*, protect cells from free radical damage, and play an important role in the prevention of cardiovascular and cerebrovascular diseases[23-25]. Our research has confirmed this effect in heart ischemia reperfusion, stroke and other diseases, and studied its mechanism. It provides experimental evidence and theoretical basis for the use of NO free radicals and natural antioxidants to protect cardiovascular and cerebrovascular Qi-blood flow, prevent cardiovascular and cerebrovascular diseases, and protect cardiovascular and cerebrovascular health.

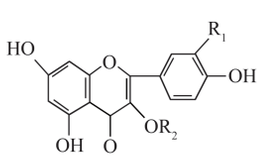
It was found that EGb 761 and Chinonin had scavenging effects on oxygen free radicals and its antioxidant properties were responsible for its

cardioprotective effects against myocardial ischemia-reperfusion injury[12,23] and that EGb 761 and Chinonin also could inhibit acute hypoxic pulmonary vasoconstriction and prevent hypoxia-induced increase of mean pulmonary arterial pressure by blocking the action of endothelin-1 and/or platelet activating factor. EGb 761 and Chinonin significantly decreased the rates of apoptotic and necrotic cardiomyocytes, and inhibited the leakage of LDH. It also diminished NO_2^-/NO_3^- and TBARS, down-regulated the expression level of p53 protein, and up-regulated bcl-2 protein, respectively. The results suggest that EGb 761 and Chinonin has preventive effects against apoptotic and necrotic cell death and its protective mechanisms are related to the antioxidant properties of scavenging oxygen free radicals, and the modulating effects on the expression levels of bcl-2 and p53 proteins[24].

We also found that the effect of Crataegus fl avonoids (CF) could scavenge oxygen free radical and increased the available NO. Thus improving levels of NO by pretreatment with CF might alleviate the outcome of IR *via* improving the blood supply through the relaxing blood vessel and preventing platelet congregation[25].

2.2 Regulatory effect of natural antioxidant ginkgo flavone on NO production during cardiac ischemia−reperfusion

Ginkgo biloba is flat in nature and tastes sweet, bitter and astringent (Figure 3). Ginkgo biloba extract has obvious effect on treating coronary heart disease, angina pectoris and hyperlipidemia. It can significantly improve dizziness, chest tightness, palpitation, shortness of breath, fatigue and other symptoms of patients with coronary heart disease[26]. It can improve cardiac blood flow, protect ischemic myocardium, reduce cholesterol, triglyceride, increase high density lipoprotein and improve hemorheology. Some studies have shown that Ginkgo biloba extract has certain anti-bacterial and anti-bacterial effects in the oral cavity, and its role in enhancing immunity and promoting apoptosis of cancer cells has a certain effect on oral cancer. It is also reported that Ginkgo biloba extract can inhibit the carcinogenic effect of nitrosamines and other substances[27-28].



R_1	R_2	
H	H	$C_{15}H_{10}O_6$
OH	H	$C_{15}H_{10}O_7$
OCH_3	H	$C_{16}H_{12}O_7$

Fig. 3 Ginkgo leaves as a source for Chinese traditional medicine and structure of the effective component ginkgo flavone in EGB 761

We have studied the cardio-protective effects of EGb 761 isolated from Ginkgo leaves and effects on the generation of NO from the injury of myocardial ischemia-reperfusion of male Wistar rats *in vivo*[22]. The results show that EGb 761 at 100 mg/kg significantly increase the levels of NO generated in the ischemia-reperfusion myocadiums and the concentration of serum thiobarbituric acid reaction substance (TBARS), the activity of creatine kinase (CK) and the rates of ventricular arrhythmia were significantlydecreased (Table 2).

Table 2 Protective effect of natural antioxidant ginkgo flavone on arrhythmia induced by cardiac ischemia−reperfusion injury

Group	BG	TG	VP	VF	VT	TAR/%
N	0/9	0/9	0/9	0/9	0/9	0
I	0/10	0/10	0/10	0/10	0/10	10
IR	0/16	0/16	3/16	3/16	1/16	43.75
IR+ EGb 761						
25	0/6	0/6	0/6	1/6	0/6	16.67
50	0/8	0/8	0/6	1/6	0/6	16.67
100	0/6	0/6	0/6	0/6	0/6	0.00
200	0/6	0/6	0/6	0/6	0/6	0.00
IR+SOD	1/9	0/9	1/9	0/9	0/9	22.22

BG: Bigeminy; TG: Trigemini; VP: Ventricular premature; VF: Ventricular fibrillation; VT: Ventricular tachycardia; TAR: Total arrhythmias rate; N: Normal control heart; I: Ischemia; IR: Ischemia reperfusion.

The cardio-protective effects of EGb 761 was also studied in the myocardial cells induced by hypoxia and reoxygenation[24]. It was found that hypoxia caused the increase of apoptotic rates and the release of lactate dehydrogenase (LDH), while reoxygenation not only further increased the apoptotic rates and leakage of LDH, but also induced necrosis of cardiomyocytes. In addition, hypoxia increased the levels of NO_2^-/NO_3^- and TBARS, while reoxygenation decreased NO_2^-/NO_3^-, but further increased TBARS in the cultured media. Moreover,

hypoxia up-regulated the expression levels of bcl-2 and p53 proteins, while reoxygenation down-regulated bcl-2 and further up-regulated p53. EGb 761 significantly decreased the rates of apoptotic and necrotic cardiomyocytes, and inhibited the leakage of LDH. It also diminished NO_2^- /NO_3^- and TBARS, down-regulated the expression level of p53 protein, and up-regulated bcl-2 protein, respectively. The results suggest that EGb 761 has preventive effects against apoptotic and necrotic cell death and its protective mechanisms are related to the antioxidant properties of scavenging oxygen free radicals, and the modulating effects on the expression levels of bcl-2 and p53 proteins (Table 3).

Table 3 Protective effect of natural antioxidant ginkgo flavone on myocardial cells induced by hypoxia and reoxygenation

Group	NO_2^- / NO_3^-	TBARS	LDH
Control	2.47 ± 0.09	4.10 ± 2.01	2.60 ± 0.31
HO	14.28 ± 0.78	5.33 ± 0.43	7.82 ± 0.47
HR	12.34 ± 0.47	7.41 ± 0.34	12.4 ± 0.66
HR + EGb	761（g/L）		
1	6.01 ± 0.53	3.65 ± 0.25	9.32 ± 0.68
10	4.61 ± 0.21	4.71 ± 0.21	7.30 ± 0.17
100	2.98 ± 0.23	4.18 ± 0.22	4.95 ± 0.22

HO: hypoxia; HR: hypoxia-reoxygenation.

2.3 Promoting effect of natural antioxidant Chinonin on NO production during cardiac ischemia−reperfusion

Rhizoma anemarhenea has been used as CTM for several thousand years (Figure 4). It can clear "heat" and purging "fire", nourish Yin and moisten dryness according traditional Chinese medicine theory. It also has been used to treat fever and thirst, liver, lung, heat and dry cough, hot bone steaming, internal heat and thirst dissipation, intestinal dryness and constipation. Chinonin is an effective component (2- (-D-glucopyranosyl-1, 3, 6, 7-tetrahydroxyl-9H-xanthin-9-tone) isolated from *Rhizoma anemarhenea*[24,29].

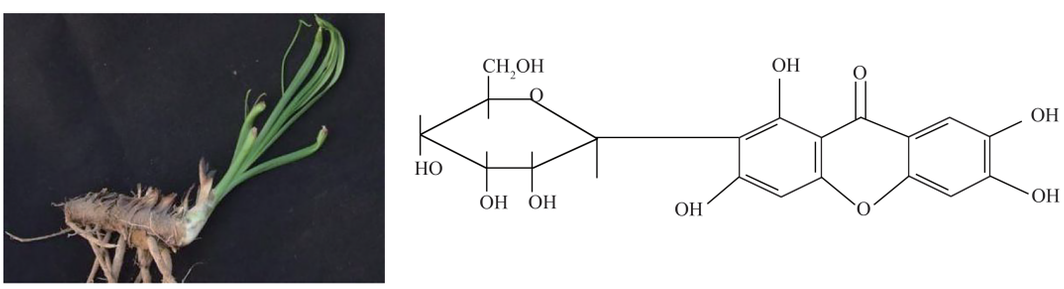


Fig.4 *Rhizoma anemarhenea* as a Chinese traditional medicine and the structure of the effective component Chinonin

The cardio-protective effects of Chinonin on the generation of NO from the injury of ischemia-reperfusion were investigated in myocardial ischemia-reperfusion injury of male Wistar rats *in vivo*. The results show that Chinonin at 5-50 mg/kg significantly increased the levels of NO generated in the ischemia-reperfusion myocadiums, scavenged oxygen free-radical and inhibited the formation of the concentration of serum TBARS, the activity of CK and the rates of ventricular arrhythmia (Table 4) [24].

The inhibitory effects of Chinonin on apoptotic and necrotic cell death of cardiomyocytes in hypoxia-reoxygenation process were observed and it was found that hypoxia caused the increase of apoptotic rates and the release of LDH, while reoxygenation not only further increased the apoptotic rates and leakage

Table 4 Protective effect of natural antioxidant Chinonin on arrhythmia induced by cardiac ischemia−reperfusion

Group	BG	TG	VP	VF	VT	TAR/%
N	0/9	0/9	0/9	0/9	0/9	0
I	0/10	0/10	0/10	0/10	0/10	10
IR	0/16	0/16	3/16	3/16	1/16	43.75
IR+CH						
5	0/6	0/6	0/6	1/6	0/6	16.67
10	0/6	0/6	0/6	0/6	0/6	0.00
25	0/6	0/6	0/6	0/6	0/6	0.00
50	0/6	0/6	0/6	0/6	0/6	0.00

BG: Bigeminy; TG: Trigemini; VP: Ventricular premature; VF: Ventricular fibrillation; VT: Ventricular tachycardia; TAR: Total arrhythmias rate; N: Normal control heart; I: Ischemia; IR: Ischemia reperfusion; CN: Chinonin (5, 10, 25, 50 mg/kg, i.p.).

of LDH, but also induced necrosis of cardiomyocytes. In addition, hypoxia increased the levels of NO_2^- / NO_3^- and TBARS, while reoxygenation decreased NO_2^- /NO_3^- , but further increased TBARS in the cultured media. Moreover, hypoxia up-regulated the expression levels of bcl-2 and p53 proteins, while reoxygenation down-regulated bcl-2 and further up-regulated p53. Chinonin significantly decreased the rates of apoptotic and necrotic cardiomyocytes, and inhibited the leakage of LDH. It also diminished NO_2^-/NO_3^- and TBARS, down-regulated the expression level of p53 protein, and up-regulated bcl-2 protein, respectively. The results suggest that Chinonin has preventive effects against apoptotic and necrotic cell death and its protective mechanisms are related to the antioxidant properties of scavenging oxygen free radicals, and the modulating effects on the expression levels of bcl-2 and p53 proteins (Table 5)[24].

Figure 5 is a summary of the mechanisms of the protective effects of EGb 761 and Chinonin on myocardial cell injury induced by ischemia (hypoxia) and reperfusion (reoxygenation). When myocardial cell was under ischemia (hypoxia) reperfusion (reoxygenation), ROS and NO are produced simultaneously to form peroxynitrite, which can damage cardiac myocytes, lipid peroxidation of cell membranes, release CK and LDH, and lead to extreme arrhythmia. Cardiomyocyte apoptosis can also be induced by the signal Bcl-2 and P53. EGb and Chinonin can prevent myocardial cell damage caused by peroxynitrite formation through scavenging ROS and preserving NO.

Table 5　Protective effect of Chinonin on myocardial cell injury induced by hypoxia and reoxygenation

Group	NO_2^- / NO_3^-	TBARS	LDH
Control	2.47 ± 0.09	4.10 ± 2.01	2.60 ± 0.31
HO	14.28 ± 0.78	5.33 ± 0.43	7.82 ± 0.47
HR	12.34 ± 0.47	7.41 ± 0.34	12.4 ± 0.66
HR+CN（g/L）			
1	6.25 ± 0.58	3.65 ± 0.25	9.32 ± 0.68
10	4.26 ± 0.36	4.71 ± 0.21	7.30 ± 0.17
100	3.20 ± 0.35	4.18 ± 0.22	5.35 ± 0.53

HO: hypoxia; HR: hypoxia-reoxygenation; CN: Chinonin (5, 10, 25, and 50 mg/kg, i.p.).

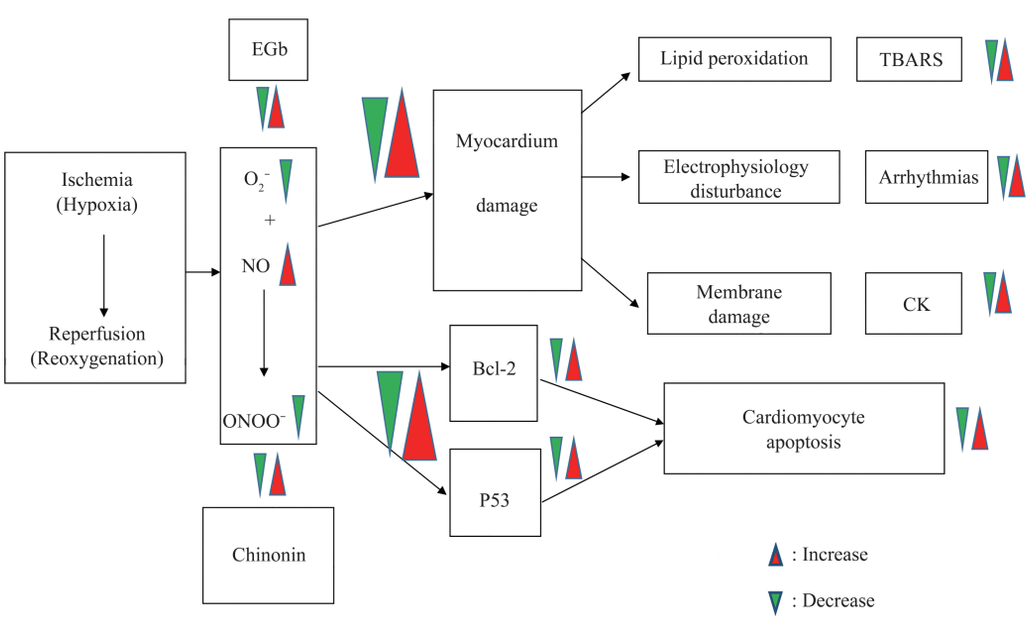


Fig. 5　The mechanisms of the protective effects of EGb 761 and Chinonin on myocardial cell injury induced by ischemia（hypoxia）and reperfusion（reoxygenation）

2.4　The effect of natural antioxidant Crataegus flavonoids on NO production in stroke

Crataegus has the effects of digestion and accumulation, promoting Qi and dissipating blood stasis (Figure 6). Crataegus is mainly used to treat dietary stagnation, diarrhea and abdominal pain,

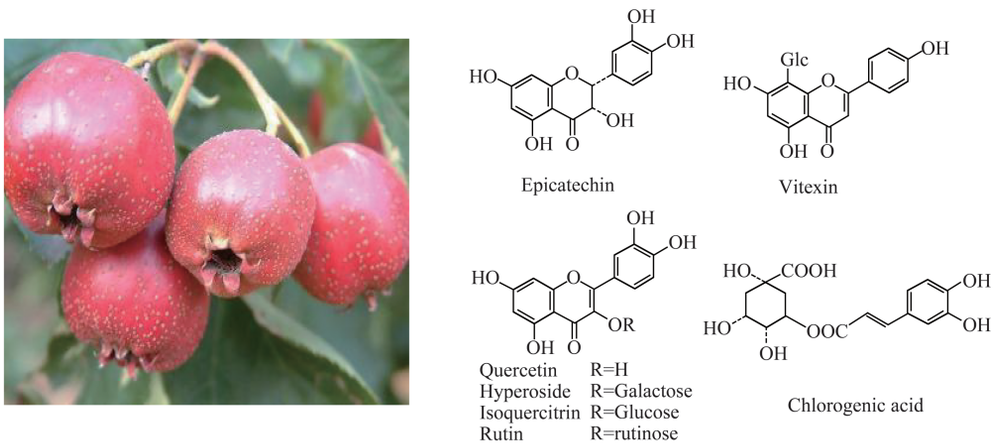


Fig. 6　Chinese traditional medicine *Crataegus* and the structure of effective component Crataegus flavonoids

hernia pain, blood stasis obstruction chest and abdominal pain, dysmenorrhea. Crataegus flavonoids is a natural antioxidant extract from Crataegus.

Stroke is a major cause of death and disability in the world; it is the third leading cause of death and the primary cause of long-term disability in adult. One of the important mechanisms in the pathogeny of stroke is free radical production during the reperfusion period, therefore we studied the effects of natural antioxidant Crataegus fl avonoids (CF), on brain ischemic insults in Mongolian gerbil stroke model. Nissl staining results showed that hippocampal CA1 pyramidal neuron was seriously damaged after ischemic for 6 days. After pretreatment of the animals with CF, the damage was improved markedly in low dose and high dose (Figure 7a). TUNEL-negative of the pyramidal cells of CA1 region from IR group shown that pretreatment with CF decreased the TUNEL-positive cell in a concentration-dependent manner, suggesting DNA was protected against IR damage (Figure 7b). It also decreased ROS production, TBARS content, and nitrite/nitrate concentration in brain homogenate, increased the brain homogenate-associated antioxidant level in a dose-dependent manner. CF pretreatment increased the amount of biologically available NO by scavenging of superoxide anion produced during reperfusion. At same time, in the process of ischemia/reperfusion brain damage, the content of nitrite/nitrate increased, while the content of NO decreased. Oral pretreatment with CF decreased the nitrite/nitrate content in the brain homogenate and increased the

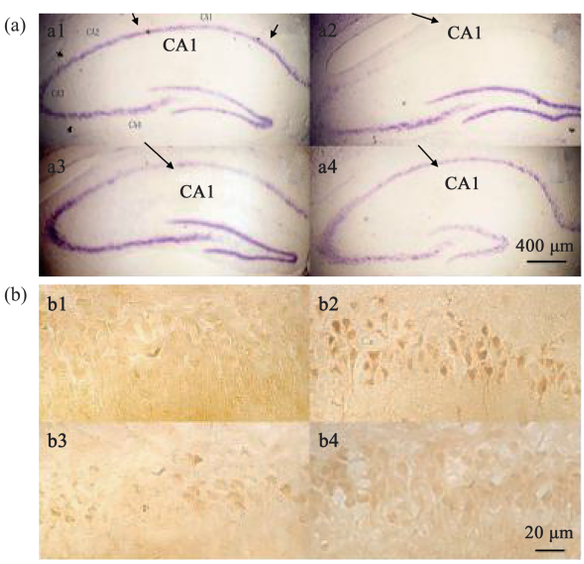


Fig. 7　Protective effects of CF on hippocampal neurons in ischemia/reperfusion brain

(a) Nissl staining of hippocampal CA1 pyramidal neuron 6 days after 5 min ischemic damage; (b) TUNEL staining of hippocampal CA1 pyramidal neuron 6 days after 5 min ischemic damage. (a1, b1) Sham group; (a2,b2) IR group; (a3,b3) low-; and (a4,b4) high-dose group.

biologically available NO concentration in a dose-dependent manner. The increasing effect of antioxidant on NO might be due to its scavenging effect on superoxide anion, which could react with NO into peroxynitrite. iNOS was implied in delayed neuron death after brain ischemic damage and it was found that pretreatment with CF could decrease the protein level of tumor necrosis factor (TNF) - α and

nuclear factor-kappa B (NF- κB), and increase the mRNA level of NOS estimated by Western blotting and RT-PCR. More neurons survived and fewer cells suffered apoptosis in the hippocampal CA1 region of CF treated animal brain. These results suggest that oral administration of this antioxidant increases the antioxidant level in the brain and protects the brain against delayed cell death caused by ischemia/reperfusion injury. By the way, CF increase the production of NO in the brain, but inhibit the expression of iNOS, which may promote the production and release of NO by increasing the expression of eNOS and nNOS[24]. After pretreatment with CF, the GSH level increased in the brain, GSH might represent a means of storing NO in a readily accessible form. The association with GSH could allow the slow release of NO into the extracellular environment and limit the inhibition of respiration by NO.

2.5 Promotion of NO production by endothelial cells by natural antioxidant L−theanine

L-theanine is known as a "natural sedative". It is a unique amino acid in tea and one of the main flavoring substances of green tea. It has a special fresh taste and can alleviate the astringency of tea. It is one of the important indicators for evaluating the quality of green tea. Many biological activities of L-theanine, such as inhibition of caffeine-induced excitation and sedation, have been widely recognized. In recent years, with the further study of its mechanism of action, L-theanine has been found to have antioxidant and neuroprotective effects[30]. Consumption of tea improves vascular function and is linked to lowering the risk of cardiovascular disease.

Siamwala JH *et al*.[31] have found that L-theanine can promote NO production in endothelial cells. L-theanine induced NO production was partially attenuated in presence of L-NAME or L-NIO and completely abolished using eNOS siRNA. eNOS activation was Ca^{2+} and Akt independent, as assessed by fluo-4AM and immunoblotting experiments, respectively and was associated with phosphorylation of eNOS Ser 1177. eNOS phosphorylation was inhibited in the presence of ERK1/2 inhibitor, PD-98059 and partially inhibited by PI3K inhibitor, LY-294002 and Wortmanin suggesting PI3K-ERK1/2 dependent pathway. Increased NO production was associated with vasodilation in *ex novo* (chorioallantoic membrane) model. These results demonstrated that L-theanine administration *in vitro* activated ERK/eNOS resulting in enhanced NO production and thereby vasodilation in the artery. The results of the experiments are suggestive of L-theanine mediated vascular health benefits of tea.

They also have found L-theanine promotes NO production in human umbilical vein and bovine aortic endothelial cells. Treatment of endothelial cells with L-theanine dose-dependently increases eNOS phosphorylation. This increase occurs at 2−5 min of L-theanine treatment and coincides with NO production. L-Theanine prevented apoptosis caused by H_2O_2 and mediated NO production induces vasodilation. L-theanine can enhance innate immune function by regulating the secretion of immune cytokines. High-dose L-theanine administration increases the levels of dopamine and 5-hydroxytryptamine in the pituitary and hippocampus, resulting in decrease in corticosterone level in the serum. After being absorbed into the body, L-theanine can penetrate the blood-brain barrier and regulate the secretion of neurotransmitters of central nervous system cells and levels of hormones such as corticosterone (CORT) and adrenaline (EPI) in the serum. L-theanine can increase levels of 5-hydroxytryptamine (5-HT) and noradrenaline, and decrease levels of adrenocorticotropic hormone and CORT in the hippocampus and prefrontal cortex of rats. L-theanine has been implicated in reduction of blood pressure in hypertensive rats. L-theanine could inhibit the glucose uptake by downregulating the related gene expression in the small intestine of rats. Intestinal gene expression of transporters responding to amino acids absorption was stimulated by L-theanine administration.

2.6 Taking cocoa polyphenols decrease blood pressure and increases nitric oxide

A designed a randomized, controlled, investigator blinded, parallel-group trial involved 44 adults aged 56 through 73 years (24 women, 20 men) with untreated upper-range prehypertension or stage 1 hypertension without concomitant risk factors. The trial was conducted at a primary care clinic in Germany between January 2005 and December 2006. From baseline to 18 weeks, dark chocolate intake reduced mean systolic blood pressure by 2.9 mmHg (mercury column) ($P<0.001$) and diastolic BP by 1.9 mmHg ($P<0.001$) without changes in body

weight, plasma levels of lipids, glucose. Hypertension prevalence declined from 86% to 68%. The blood pressure decrease was accompanied by a sustained increase of *S*-nitrosoglutathione by 0.23 nmol/L ($P<0.001$). Dark chocolate dose resulted in the appearance of cocoa phenols in plasma. But white chocolate intake caused no changes in blood pressure or plasma biomarkers[32].

3 Synergistic protective and promotive effectsof natural antioxidants and NO free radicalon cardiovascular and cerebrovascular health

According to the above ideas, we have screened and optimized a set of formula. It can not only produce NO, but also protect NO. It can also regulate blood lipids, blood sugar and blood pressure, prevent heart and cerebral ischemia injury, Alzheimer's disease.

The guidelines for designing the formula are: a. Natural, safe and effective; b. Protecting and increasing the advantages of NO, reduce and avoid the risk of NO; c. The combination of Chinese and the West medicines; and d. Promoting Qi-blood circulation and removing blood stasis, reducing blood lipid and blood sugar. The formula consists of L-arginine, Crataegus extract, *Rhizoma anemarhenea,* extract and astaxanthin.

3.1 The formula has obvious scavenging effect on oxygen free radicals and decreasing the increases of blood lipid，blood sugar and blood pressure

It was found that the formula could effectively scavenge hydroxyl, superoxide free radicals and decrease the increases of blood lipid, blood sugar and blood pressure caused by higher lipid food and genetic factors in animals, suggesting that suitable formula can protect blood against the damage caused by higher lipid food and genetic factors[33].

3.2 The formula has obvious inhibitory effect on pulmonary enlargement induced cell damage and rat heart ischemia damage by intraperitoneal injection of isoproterenol

The preventive effects of formula on heart cell against pulmonary enlargement induced H9C2 cell damage and isoproterenol induced ischemia heart damage of rats were studied. It was found that a suitable low concentration of NO generated from L-arginine could protect H9C2 cell against the damage by PE. The formula could decrease PE treated cell damage, by scavenging ROS generated in the cell caused by PE; It also found that the formula could decrease the Isoproterenol (ISO) induced heart ischemia damage in rats (Table 5). It suggests that the formula of NO and natural antioxidants might be used to prevent and cure myocardial infarction[32], besides other CTM for instance lumbrokinase[34].

Table 5 NO protected the heart and lung against damage caused by Isoproterenol

Index	Control	ISO	ISO+formula
Body weight（g）	27.40±0.74	27.99±1.02	27.16±0.71
Heart weight（g）	0.1018±0.0044	0.1582±0.0016*	0.1114±0.0033#
Lung weight（g）	0.1482±0.0073	0.1722±0.0049*	0.1510±0.0051#
Heart/body（mg/g）	3.74±0.23	5.67±0.15*	4.11±0.14#
Lung/body（mg/g）	5.40±0.16	6.19±0.33*	5.58±0.27
Spray blood by heart	67.5±0.88	48.3±0.36*	59.4±0.98

ISO : Isoproterenol ; *$P<0.05$ *vs* control, # $P<0.05$ *vs* ISO group.

3.3 The formula has protective effect of NO on brain against ischemia−reperfusion damage

The preventive and cure effects of the formula on stroke in oxygen and glucose deprivation (OGD) treated cell and local brain ischemia of mouse were studied. It was found that the formula of NO and natural antioxidants could decrease OGD treated cell damage, scavenge ROS generated in the cell caused by OGD, protect mitochondrial membrane and modulate the express of apoptosis related proteins Bcl-2, Baxand Caspase-3; It was also found that the formula could decrease the local brain ischemia induced mouse stroke behavior, cell apoptosis and express of related proteins Bcl2 and Bax. It suggests that the formula of NO and natural antioxidants might prevent and cure stroke[35].

3.4 The formula has significant protective effect on the paralysis behavior of nematodes in animals with Alzheimer´s disease induced by A−beta

The preventive and therapeutic potential of NO and the formula on Alzheimer's disease (AD) were studied using transgenic cells and *C. elegans* models. It was found that low concentration of NO protected neuronal cells by reducing the production of ROS. Low concentration of the formula could protect *C. elegans* against paralysis induced by expression of

transgenic A-beta gene. It was found that the formula also increased the viability of N2a cells overexpressing APPswe and ApoE4 by scavenging ROS. These results suggest that the formula may have a potential for prevention and treatment of AD[36-37].

4 Natural antioxidants and nitric oxide can synergistically eliminate the damage caused by inflammation

We have studied a variety of antioxidants, especially natural antioxidants, and found that antioxidants could effectively eliminate harmful free radicals[19]. Some Chinese herbal medicines also contain a lot of natural antioxidants, which can also effectively eliminate the harmful free radicals produced by inflammation, protect cells and tissues, and prevent free radical damage[36]. We studied the synergistic preventive effect of nitric oxide and antioxidant on pulmonary function injury induced by PM2.5, and found that the product can significantly reduce the inflammatory factors IL-1 β and IFN-α in mice, significantly reduce the apoptosis in mice lung, alleviate the thickening and damage of tracheal wall caused by PM2.5, and also reduce the degree of pulmonary fibrosis, indicating that it has the protective effect on pulmonary function and lung inflammation.

5 Nitric oxide and natural antioxidants prolong the longevity of nematodes

5.1 Bacterial nitric oxide extends the lifespan of *C. elegans*

Nitric oxide is an important signal molecule in multicellular organisms. Most animals produce NO from L-arginine *via* a family of dedicated enzymes known as NO synthases. A rare exception is the roundworm *C. elegans*, which lacks its own NOS. However, in its natural environment, *C. elegans* feeds on Bacilli that possess functional NOS. Gusarov and coworkers demonstrated that bacterially derived NO enhances *C.elegans* longevity and stress resistance *via* a defined group of genes that function under the dual control of heat shock protein (HSF-1) and DAF-16 transcription factors. Their work provides an example of interspecies signaling by a small molecule NO and illustrates the lifelong value of commensal bacteria to their host[38].

5.2 Natural antioxidants extends the lifespan of *C. elegans*

The benefits of tea for human health are widely accepted all over the world. Epigallocatechin gallate (EGCG) (Figure 8), a main active ingredient of green tea, is believed to be beneficial in association with anti-carcinogenesis, anti-obesity, anti-Parkinson's disease, anti-diabetesand blood pressure reduction[39-44]. Here we found that EGCG extended *C. elegans* longevity under stress. Under heat stress (35℃), EGCG improved the mean longevity by 13.1% at 0.1 mg/L, 8.0% at 1.0 mg/L, and 11.8% at 10.0 mg/L respectively. Under oxidative stress, EGCG could improve the mean longevity of *C. elegans* by 172.9% at 0.1 mg/L, 177.7% at 1.0 mg/L, and 88.5% at 10.0 mg/L respectively. However, EGCG could not extend the life span of *C. elegans* under normal culture conditions. Further studies demonstrated that the significant longevity-extending effects of EGCG on *C. elegans* could be attributed to its *in vitro* and *in vivo* free radical-scavenging effects and its up-regulating effects on stress-resistance-related proteins,

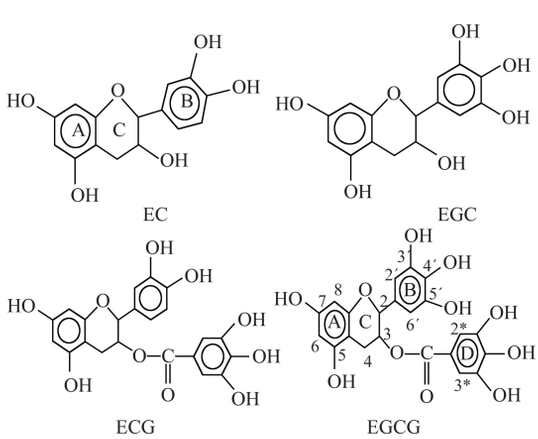


Fig. 8 Tea and structures of polyphenols in green tea

including superoxide dismutase-3 (SOD-3) and heat shock protein-16.2 (HSP-16.2), in transgenic *C. elegans* with SOD-3 ∷ green fluorescentprotein (GFP) and HSP-16.2 ∷ GFP expression. Quantitative real-time PCR results showed that the up-regulation of aging-associated genes such as daf-16, sod-3, and skn-1 could also contribute tothe stress resistance attributed to EGCG. As the death rate of a population is closely related to the mortality caused by external stress, it could be concluded that the survival-enhancing effects of EGCG on *C. elegans* under stress are very important for antiaging research[45].

Tetrapeptide (Leu-Asp-Tyr-Glu) and from maize (TPM) and dipeptide Tyr-Ala (TA) is a bioactive peptide. We found that TPM extended the lifespan of *C. elegans* under heat and oxidative stress. Specifically, TPM (10 mmol/L) increased the average longevity of *C. elegans* by 36.9% and 27.6% under the heat stress (35℃) and oxidative stress respectively. Further studies demonstrated that the significant longevity-extending effects of TPM on *C. elegans* could be attributed to its *in vitro* and *in vivo* free radical-scavenging effects and its up-regulation of stress-resistance-related proteins, including superoxide dismutase-3 (SOD-3) and heat shock protein-16.2 (HSP-16.2). Real-time PCR results showed that the up-regulation of aging-associated genes such as daf-16, sod-3 and hsp-16.2, in addition to skn-1, ctl-1 and ctl-2 could also contribute to the stress-resistance effect of TPM. These results indicated that TPM can (or has potential to) protect against external stress and extend the lifespan under stress[46-47].

We also found that L-theanine improves stress resistance in *C. elegans* could significant increased longevity of *C. elegans* about 12.8% and 21.3% under heat stress and oxidative stress respectively[48].

Quinic acid (QA) is an active ingredient of Cat's Claw (Uncaria tomentosa), which is found to be active in enhancing DNA repair and immunity in model systems and able to generate neuroprotective effects in neurons. We found that QA could provide protectiveeffect in *C. elegans* and improve worm survival under stress. Under heat stress and oxidative stress, QA-treated wild-type *C. elegans* N2 survived 17.8% and 29.7% longer, respectively, than the control worms. Our data suggest that under heat stress, QA can upregulate the expression of the small heat shock protein hsp-16.2 gene, which could help the worms survive a longer time. We also found that QA extended the *C. elegans* mutant VC475 [hsp-16.2 (gk249)] life span by 15.7% under normal culture conditions. However, under normal culture conditions, QA did not affect hsp-16.2 expression, but upregulated the expression of daf-16 and sod-3 in a DAF-16 - dependent manner, and downregulated the level of reactive oxygen species (ROS), suggesting that under normal conditions QA acts in different pathways. As a natural product, QA demonstrates great potential as a rejuvenating compound[49].

6 Traditional Chinese medicines including natural antioxidants ensure health by activating blood circulation and removing blood stasis

Natural antioxidants can scavenge oxygen free radicals, protect NO free radicals, make Qi and blood unblocked, protect cardiovascular and cerebrovascular health, prevent cardiovascular and cerebrovascular diseases. A large number of experimental evidence shows that the active ingredients of some traditional Chinese medicines are natural antioxidants.

Qi Shen Yi Qi Pills (QSYQ) is a compound Chinese medicine widely used in China for treatment of cardiovascular disease[44]. Zheng QN *et al*.[50] investigated the effect of post-treatment with QSYQ on myocardial fibrosis after I/R-induced myocardium injury, and the role of different compounds of QSYQ, focusing especially on the involvement of chemokine ribosomal protein S19 (RP S19) dimer and monocyte migration. Male Sprague-Dawley rats were subjected to left anterior descending coronary artery occlusion for 30 min followed by reperfusion with or without administration of QSYQ once daily by gavage for 6 days. They found that post-treatment with QSYQ diminished I/R-induced infarct size, alleviated myocardium injury, attenuated myocardial fibrosis after 6 days of reperfusion, and restored heart function and myocardial blood flow after I/R. In addition, the drug significantly inhibited monocyte infiltration and macrophage polarization towards M2, which was attributable to chemokine RP S19 dimer. Moreover, Western blots revealed that QSYQ blocked I/R-induced increase in TGFβ1 and TGFβRIIand reversed its relevant gene expression, such as Smad3,4,6,7, and inhibited the increase of MMP 2, 9 expression. The results provide evidence for the potential role of

QSYQ in treating myocardial fi brosis following I/R injury[50].

Cardiac Qi deficiency and stasis of blood is common symptom of IR-inducedmyocardial injury and cardiac hypertrophy, which is often treated by invigorating Qi and activating blood. Qi Shen Yi Qi Pills (QSYQ), a compound Chinese medicine with potential of invigorating Qi and activating blood, is used for treating Qi deficiency and stasis of blood-caused angina pectoris and coronary heart disease. Han[51] used cardiacI/Rinjury or pressure over-load induced cardiac hypertrophy in a rata model and partly clarified the scientific connotation of cardiac Qi deficiency and stasis of blood. The study coveredcardiac energy metabolism, mitochondria complexes and subunits, histone deacetylase Sirt1, small G protein RhoA/ROCK, cytoskeleton, cardiacfunction and dynamic characteristics of the microcirculation[52]. The results disclosed the mechanisms of QSYQ's effect and the rationale behind synergistic effect of major ingredients, providing support for application of QSYQ intreatment of cardiacI/Rinjury and hypertrophy [51].

7 Conclusion

From above discussion, NO free radical is a driving force of microcirculation Qi and blood patency. Natural antioxidants can protect and promote NO production, and ensure microcirculation patency and protect health together with NO. NO and natural antioxidants prolong the longevity of nematodes. Traditional Chinese medicines including natural antioxidants ensure health by activating blood circulation and removing blood stasis.

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一氧化氮自由基是气血通畅的驱动力*

赵保路**

（中国科学院生物物理研究所，北京 100101）

摘要　一氧化氮（NO）自由基是气血通畅的动力之一；抗氧化剂清除氧自由基，保护NO并且能够协助NO共同促进气血通畅，预防和保护心脑血管的健康；NO和天然抗氧化剂可以延缓衰老，还可以协同预防和治疗炎症引起的损伤；包含天然抗氧化剂的中草药，促进气血通畅，溶化血栓，是中草药通过一氧化氮自由基活血化瘀的机理.

关键词　一氧化氮，氧自由基，天然抗氧化剂，中草药

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** 通讯联系人.

Tel：13681023252，E-mail：zhaobl@sun5.ibp.ac.cn

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