Nutrition and Nutraceutical Supplements for the Treatment of Hypertension: Part III

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Vascular biology, endothelial and vascular smooth muscle, and cardiac dysfunction play a primary role in the initiation and perpetuation of hypertension, cardiovascular disease, and target organ damage. Nutrient-gene interactions and epigenetics are predominant factors in promoting beneficial or detrimental effects in cardiovascular health and hypertension. Macronutrients and micronutrients can prevent, control, and treat hypertension through numerous mechanisms related to vascular biology. Oxidative stress, inflammation, and autoimmune dysfunction initiate and propagate hypertension and cardiovascular disease. There is a role for the selected use of single and component nutraceutical supplements, vitamins, antioxidants, and minerals in the treatment of hypertension based on scientifically controlled studies that complement optimal nutrition, coupled with other lifestyle modifications. *J Clin Hypertens (Greenwich).* 2013;15:931–937.

In parts I and II of this series, pathophysiology, nutrition, minerals, specific food groups, and some nutraceutical supplements that are effective in reducing blood pressure (BP) and improving vascular and endothelial function were reviewed. In this last part, the review will be completed by discussing nutritional supplements that have been investigated in human trials and how they may be used in combination or with antihypertensive drugs to reduce BP and improve vascular and endothelial function.

VITAMIN B6 (PYRIDOXINE)

Low serum vitamin B6 (pyridoxine) levels are associated with hypertension in humans.[1] One human study by Aybak and colleagues[2] proved that high-dose vitamin B6 at 5 mg/kg/d for 4 weeks significantly lowered BP by 14/10 mm Hg. Pyridoxine (vitamin B6) is a cofactor in neurotransmitter and hormone synthesis in the central nervous system (norepinephrine, epinephrine, serotonin, gamma-aminobutyric acid [GABA], and kynurenine), increases cysteine synthesis to neutralize aldehydes, enhances the production of glutathione, blocks calcium channels, decreases central sympathetic tone, and reduces end organ responsiveness to glucocorticoids and mineralocorticoids.[3,4] Vitamin B6 is reduced with chronic diuretic therapy and heme pyrollactams. Vitamin B6 thus has similar action to central α-agonists, diuretics, and calcium channel blockers. The recommended dose is 200 mg/d orally.

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FLAVONOIDS

More than 4000 naturally occurring flavonoids have been identified in such diverse substances as fruits, vegetables, red wine, tea, soy, and licorice.[5] Flavonoids (flavonols, flavones, and isoflavones) are potent free radical scavengers that inhibit lipid peroxidation, prevent atherosclerosis, promote vascular relaxation, and have antihypertensive effects.[5,6]

Resveratrol is a potent antioxidant and antihypertensive found in the skin of red grapes and red wine. Resveratrol administration to humans reduces augmentation index, improves arterial compliance, and lowers central arterial pressure when administered at 250 mL of either regular or dealcoholized red wine.[7] Central arterial pressure has been shown to be significantly reduced by dealcoholized red wine at 7.4 mm Hg and 5.4 mm Hg by regular red wine. Resveratrol increases flow-mediated vasodilation in a dose-related manner, improves endothelial dysfunction, prevents uncoupling of endothelial nitric oxide synthase (eNOS), increases adiponectin, lowers high-sensitivity C-reactive protein (hs-CRP), and blocks the effects of angiotensin II.[7,8] The recommended dose is 250 mg/d of trans-resveratrol.[8]

LYCOPENE

Lycopene is a fat-soluble carotenoid found in tomatoes, guava, pink grapefruit, watermelon, apricots, and papaya in high concentrations that shows a significant reduction in BP and oxidative stress markers in most studies.[9–13] Paran and colleagues[13] administered 10 mg of lycopene to patients with grade I hypertension during 8 weeks with a reduction in BP of 9/7 mm Hg ($P<.01$). A tomato extract given to 31 hypertensive patients reduced BP reduction 10/4 mm Hg.[10] Patients taking various antihypertensive agents including angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCBs), and diuretics had additional BP reduction of 5.4/3 mm Hg in 6 weeks when administered a standardized

tomato extract.[11] Lycopene and tomato extract improve endothelial dysfunction and reduce plasma total oxidative stress.[9–13] The recommended daily intake of lycopene is 10 mg to 20 mg in food or supplement form.

PYCNOGENOL

Pycnogenol, a bark extract from the French maritime pine, at doses of 200 mg/d have been shown to reduce BP 7.2/1.8 mm Hg ($P<.05$).[14–16] Pycnogenol acts as a natural ACE inhibitor, protects cell membranes from oxidative stress, increases nitric oxide, and improves endothelial function, and decreases hs-CRP.[14–16] Other studies have shown reductions in BP and a decreased need for ACE inhibitors and CCBs and decreased endothelin-1 (ET-1) and myeloperoxidase.[14–16]

GARLIC

Clinical trials have shown consistent reductions in BP with garlic in hypertensive patients with an average reduction in BP of 8.4/7.3 mm Hg.[17–19] Cultivated garlic (*Allium sativum*), wild uncultivated garlic or bear garlic (*Allium urisinum*), and aged garlic are the most effective.[17–19] Garlic is also effective in reducing BP in patients with uncontrolled hypertension already taking antihypertensive medication.[17–19] A garlic homogenate-based supplement was administered to 34 prehypertensive and stage I hypertensive patients at 300 mg/d during 12 weeks with a reduction in BP of 6.6 mm Hg to 7.5/4.6 mm Hg to 5.2 mm Hg.[18] Aged garlic at doses of 240 mg/d to 960 mg/d given to 79 hypertensive patients during 12 weeks significantly lowered systolic BP (SBP) 11.8±5.4 mm Hg in the high-dose garlic group.[19] The overall net reduction in BP was 10 mm Hg to 12/6 mm Hg to 9 mm Hg in all clinical trials with garlic.[17–19] Garlic has ACE inhibitor activity and calcium channel–blocking activity and reduces catecholamine sensitivity, improves arterial compliance, and increases bradykinin and nitric oxide.[1,17–19]

SEAWEED

Wakame seaweed (*Undaria pinnatifida*) is the most popular edible seaweed in Japan[20–22] and has been shown to significantly reduce BP 14/5 mm Hg ($P<.01$) at doses of 3.3 g/d.[21] A potassium-loaded, ion-exchange, sodium-adsorbing, potassium-releasing seaweed preparation reduced mean arterial pressure by 11.2 mm Hg ($P<.001$) in sodium-sensitive patients and 5.7 mm Hg ($P<.05$) in sodium-insensitive patients.[22]

Seaweed and sea vegetables contain most all of the seawater's 77 minerals and rare earth elements, fiber, and alginate in a colloidal form.[20–22] The primary effect of Wakame appears to be through its ACE inhibitor activity.[23] Its long-term use in Japan has demonstrated its safety.

SESAME

Sesame has been shown to reduce BP[24–31] when given alone[32–36] or in combination with nifedipine,[28] diuretics, and β-blockers.[25] A dose of 60 mg of sesamin for 4 weeks lowered BP 3.5/1.9 mm Hg ($P<.045$).[26] Black sesame meal at 2.52 g/d reduced SBP by 8.3 mm Hg ($P<.05$) but there was a nonsignificant reduction in diastolic BP (DBP) of 4.2 mm Hg.[27] Sesame oil at 35 g/d significantly lowered central BP within 1 hour and also maintained BP reduction chronically in 30 hypertensive patients with reduced heart rate, arterial stiffness, augmentation index, pulse wave velocity, hs-CRP, and ET-1 with increased nitric oxide and antioxidant capacity.[31] The active ingredients are natural ACE inhibitors such as sesamin, sesamolin, sesaminol glucosides, and furoufuran lignans, which are also suppressors of NF-κB.[30]

BEVERAGES: TEA, COFFEE, AND COCOA

Green tea, black tea, and extracts of active components in both have demonstrated reduction in BP in humans.[37–41] In a double-blind, placebo-controlled trial of 379 hypertensive patients given green tea extract 370 mg/d for 3 months, BP was reduced significantly at 4/4 mm Hg with simultaneous decrease in hs-CRP.[40]

Dark chocolate (100 g) and cocoa with a high content of polyphenols (≥30 mg) have been shown to significantly reduce BP in humans.[42–48] A meta-analysis of 173 hypertensive patients given cocoa for a mean duration of 2 weeks had a significant reduction in BP 4.7/2.8 mm Hg ($P=.002$).[42] Cocoa at 30 mg of polyphenols reduced BP in prehypertensive and stage I hypertensive patients by 2.9/1.9 mm Hg at 18 weeks ($P<.001$).[43] Two more recent meta-analysis of 13 trials and 10 trials with 297 patients found a significant reduction in BP of 3.2/2.0 mm Hg and 4.5/3.2 mm Hg, respectively.[44,46]BP reduction was the greatest in patients with the highest baseline BP and those with at least 50% to 70% cocoa at doses of 6 g/d to 100 g/d.[44,46,47] Cocoa may also improve insulin resistance and endothelial function.[48]

Polyphenols, chlorogenic acids (CGAs), the ferulic acid metabolite of CGAs, and di-hydro-caffeic acids decrease BP in a dose-dependent manner, increase eNOS, and improve endothelial function in humans.[49–51] CGAs in green coffee bean extract at doses of 140 mg/d significantly reduced BP in 28 patients in a placebo-controlled randomized clinical trial.[49] A study of 122 men demonstrated a dose response in BP with doses of CGA from 46 mg to 185 mg/d.[50] The group that received the 185 mg dose had a significant reduction in BP of 5.6/3.9 mm Hg ($P<.01$). Hydroxyhydroquinone is another component of coffee beans that reduces the efficacy of CGAs in a dose-dependent manner, which partially explains the conflicting results of coffee ingestion on BP.[51] Furthermore, there is genetic variation in the enzyme responsible for the metabolism of caffeine that modifies the association between coffee intake, amount of coffee ingested, and the risk of hypertension, heart rate, myocardial infarction, arterial stiffness, arterial wave reflections, and urinary catecholamine levels.[52] A total of 59% of the population has the IF/IA allele of the

CYP1A2 genotype, which confers slow metabolism of caffeine. Heavy coffee drinkers who are slow metabolizers had a 3.00 hazard ratio (HR) for developing hypertension. In contrast, fast metabolizers with the IA/IA allele have a 0.36 HR for incident hypertension.[52]

ADDITIONAL COMPOUNDS

Melatonin demonstrates significant antihypertensive effects in humans in numerous double-blind, randomized, placebo-controlled clinical trials at 3 mg/d to 5 mg/d.[53–56] The average reduction in BP is 6/3 mm Hg. Melatonin stimulates GABA receptors in the central nervous system and vascular melatonin receptors, inhibits plasma AII levels, improves endothelial function, increases nitric oxide, vasodilates, improves nocturnal dipping, lowers cortisol, and is additive with ARBs. β-Blockers reduce melatonin secretion.[56]

Hesperidin significantly lowered DBP 3 mm Hg to 4 mm Hg ($P<.02$) and improved microvascular endothelial reactivity in 24 obese hypertensive men in a randomized, controlled crossover study during 4 weeks for each of 3 treatment groups consuming 500 mL of orange juice, hesperidin, or placebo.[57]

Pomegranate juice is rich in tannins and has numerous other effects that improve vascular health, including the reduction of SBP by 5% to 12%.[58,59] A study of 51 healthy patients given 330 mg/d of pomegranate juice had a reduction in BP of 3.14/2.33 mm Hg ($P<.001$).[59] Pomegranate juice also suppresses the postprandial increase in SBP following a high-fat meal.[59] Pomegranate juice reduces serum ACE activity by 36%, and has anti-atherogenic, antioxidant, and anti-inflammatory effects.[58–60] Pomegranate juice at 50 mL/d reduced carotid intima-media thickness by 30% during 1 year, increased paraoxonase by 83%, decreased oxidized low-density lipoprotein by 59% to 90%, decreased antibodies to oxidized LDL by 19%, increased total antioxidant status by 130%, reduced transforming growth factor β, increased catalase, superoxide dismutase and glutathione peroxidase, increased eNOS and nitric oxide, and improved endothelial function.[58–60] Pomegranate juice works like an ACE inhibitor.

Grape seed extract (GSE) was administered to patients in 9 randomized trials, a meta-analysis of 390 patients, and demonstrated a significant reduction in SBP of 1.54 mm Hg ($P<.02$).[61–63] A significant reduction in BP of 11/8 mm Hg ($P<.05$) was seen in another dose-response study with 150 mg/d to 300 mg/d of GSE during 4 weeks.[62] GSE has high phenolic content that activates the PI3K/Akt-signaling pathway that phosphorylates eNOS and increases NO.[62,63]

COENZYME Q10 (UBIQUINONE)

Coenzyme Q10 has consistent and significant antihypertensive effects in patients with essential hypertension.[64–69] Compared with normotensive patients, essential hypertensive patients have a higher incidence (6-fold) of coenzyme Q10 deficiency documented by serum levels.[64–69] Doses of 120 mg/d to 225 mg/d of coenzyme Q10 are necessary to achieve a therapeutic level of 3 μg/mL.[64–69] This dose is usually 3 mg/kg/d to 5 mg/kg/d of coenzyme Q10. Patients with the lowest coenzyme Q10 serum levels may have the best antihypertensive response to supplementation.[64–69] The average reduction in BP is about 15/10 mm Hg, and heart rate falls 5 beats per minute based on reported studies and meta-analyses.[64–69] The antihypertensive effect takes time to reach its peak level at 4 weeks. Then the BP remains stable during long-term treatment. The antihypertensive effect is gone within 2 weeks after discontinuation of coenzyme Q10. The reduction in BP and systemic vascular resistance are correlated with the pretreatment and post-treatment serum levels of coenzyme Q10. About 50% of patients respond to oral coenzyme Q10 supplementation for BP.[65]

Approximately 50% of patients taking antihypertensive drugs may be able to stop between 1 and 3 agents. Both total dose and frequency of administration may be reduced. Patients administered coenzyme Q10 with enalapril improved the 24-hour ABPM better than with enalapril monotherapy and also normalized endothelial function.[32] Coenzyme Q10 is a lipid-phase antioxidant and free radical scavenger that increases eNOS and NO, reduces inflammation and NFkB, and improves endothelial function and vascular elasticity.[66,67]

ALPHA LIPOIC ACID

Alpha lipoic acid (ALA) is a sulfur-containing compound with antioxidant activity that is effective in hypertension, especially as part of the metabolic syndrome.[33–36] In a double-blind cross-over study of 36 patients during 8 weeks with congestive heart failure and hypertension, 200 mg of lipoic acid with 500 mg of acetyl-L-carnitine significantly reduced BP 7/3 mm Hg and increased brachial artery diameter.[33] The QUALITY study of 40 patients with diabetes mellitus and stage I hypertension showed significant improvements in BP and urinary albumin excretion with a combination of quinapril (40 mg/d) and lipoic acid (600 mg/d) that was greater than either agent alone.[35] Lipoic acid increases levels of glutathione, cysteine, vitamin C, and vitamin E; inhibits NFkB; reduces ET-1, tissue factor, and vascular cell adhesion molecule 1; increases cyclic adenosine monophosphate, downregulates CD4 immune expression on mononuclear cells; reduces oxidative stress, inflammation, atherosclerosis in animal models; decreases serum aldehydes; and closes calcium channels, which improves vasodilation, increases nitric oxide, and nitrosothiols, improves endothelial function, and lowers BP.[33–36] Lipoic acid normalizes membrane calcium channels by providing sulfhydryl groups, decreasing cytosolic free calcium, and lowering systemic vascular resistance. Morcos and coworkers[36] showed stabilization of urinary albumin excretion in diabetes mellitus patients given 600 mg of ALA compared with placebo for 18 months ($P<.05$). The recommended dose is 100 mg/d to 200 mg/d of R-lipoic acid with biotin

TABLE. An Integrative Approach to the Treatment of Hypertension

Intervention Category	Therapeutic Intervention	Daily Intake
Diet characteristics	DASH I, DASH II-Na^+, or PREMIER diet	Diet type
	Sodium restriction	1500 mg
	Potassium	5000 mg
	Potassium/sodium ratio	>3:1
	Magnesium	1000 mg
	Zinc	50 mg
Macronutrients	Protein: Total intake from non-animal sources, organic lean or wild animal protein, or coldwater fish	30% of total calories/1.5–1.8 g/kg body weight
	Whey protein	30 g
	Soy protein (fermented sources are preferred)	30 g
	Sardine muscle concentrate extract	3 g
	Milk peptides (valyl prolyl proline and isoleucyl prolyl proline)	30–60 mg
	Fat	30% of total calories
	Omega-3 fatty acids	2–3 g
	Omega-6 fatty acids	1 g
	Omega-9 fatty acids	2–4 tablespoons of olive or nut oil or 10–20 olives
	Saturated fatty acids from wild game, bison, or other lean meat	<10% total calories
	Polyunsaturated to saturated fat ratio	>2.0
	Omega 3 to omega 6 ratio	1.1–1.2
	Synthetic trans fatty acids	None (completely remove from diet)
	Nuts in variety	*Ad libidum*
	Carbohydrates: as primarily complex carbohydrates and fiber	40% of total calories
	Oatmeal or	60 g
	Oatbran or	40 g
	Beta-glucan or	3 g
	Psyllium	7 g
Specific foods	Garlic as fresh cloves or aged Kyolic garlic	4 fresh cloves (4 g) or 600 mg aged garlic taken twice daily
	Sea vegetables, specifically dried wakame	3.0–3.5 g
	Lycopene as tomato products, guava, watermelon, apricots, pink grapefruit, papaya, or supplements	10–20 mg
	Dark chocolate	100 g
	Pomegranate juice or seeds	8 oz or 1 cup
	Sesame	60 mg sesamin or 2.5 g sesame meal
Exercise	Aerobic	20 min daily at 4200 KJ/wk
	Resistance	40 min/d
Weight reduction	Body mass index <25 Waist circumference: <35 in for women <40 in for men Total body fat: <22% for women <16% for men	Lose 1–2 pounds per wk and increasing the proportion of lean muscle
Other lifestyle recommendations	Alcohol restriction: Among the choice of alcohol red wine is preferred due to its vasoactive phytonutrients	<20 g/d Wine <10 oz Beer <24 oz Liquor <2 oz
	Caffeine restriction or elimination depending on CYP 450 type	<100 mg/d
	Tobacco and smoking	Stop
Medical considerations	Medications that may increase blood pressure	Minimize use when possible, such as by using disease-specific nutritional interventions
Supplemental foods and nutrients	Alpha lipoic acid with biotin	100–200 mg twice daily
	Amino acids:	
	Arginine	5 g twice daily
	Carnitine	1–2 g twice daily

TABLE. An Integrative Approach to the Treatment of Hypertension (Continued)

Intervention Category	Therapeutic Intervention	Daily Intake
	Taurine	1–3 g twice daily
	Chlorogenic acids	150–200 mg
	Coenzyme Q10	100 mg once to twice daily
	Grape seed extract	300 mg
	Hawthorne extract	500 mg twice a day
	Melatonin	2.5 mg
	N-acetyl cysteine	500 mg twice a day
	Olive leaf extract (oleuropein)	500 mg twice a day
	Pycnogenol	200 mg
	Quercetin	500 mg twice a day
	Resveratrol (trans)	250 mg
	Vitamin B6	100 mg once to twice daily
	Vitamin C	250–500 mg twice daily
	Vitamin D3	Dose to raise 25-hydroxyvitamin D serum level to 60 ng/mL
	Vitamin E as mixed tocopherols	400 IU

Abbreviation: DASH, The Dietary Approaches to Stop Hypertension.

2 mg/d to 4 mg/d to prevent biotin depletion with long-term use of lipoic acid.

N-ACETYL CYSTEINE

N-acetyl cysteine (NAC) and L-arginine (ARG) in combination significantly reduce endothelial activation and BP in hypertensive patients with type 2 diabetes mellitus.[70] In addition, hs-CRP, intercellular adhesion molecule, and vascular cell adhesion molecule were decreased while nitric oxide and endothelial postischemic vasodilation increased.[70] NAC increases nitric oxide via interleukin 1b and increases iNOS messenger RNA, increases glutathione by increasing cysteine levels, reduces the affinity for the AT_1 receptor by disrupting disulfide groups, and blocks the L-type calcium channel.[70–72] The recommended dose is 500 mg to 1000 mg twice a day.

HAWTHORNE

Hawthorne extract has been used for centuries for the treatment of hypertension, congestive heart failure, and other cardiovascular diseases.[73–75] A recent 4-period, crossover design, dose-response study in 21 patients with prehypertension or mild hypertension over 3.5 days did not show changes in fibromuscular dysplasia or BP on standardized extract with 50 mg of oligomeric procyanidin per 250 mg extract with 1000 mg, 1500 mg, or 2500 mg of the extract.[73] Patients with hypertension and type 2 diabetes mellitus taking medications for BP and diabetes mellitus were randomized to 1200 mg of hawthorne extract for 16 weeks showed significant reductions in DBP of 2.6 mm Hg (P=.035).[74] Thirty-six mildly hypertensive patients were administered 500 mg of hawthorne extract for 10 weeks and showed a nonsignificant trend in DBP reduction (P=.081) compared with placebo.[75] Hawthorne acts like an ACE inhibitor, β-blocker, CCB, and diuretic. More studies are needed to determine the efficacy, long-term effects, and dose of hawthorne for the treatment of hypertension.

QUERCETIN

Quercetin is an antioxidant flavonol found in apples, berries, and onions that reduces BP in hypertensive individuals,[76–78] but the hypotensive effects do not appear to be mediated by changes in hs-CRP, tumor necrosis factor α, ACE activity, ET-1, NO, vascular reactivity, or flow-mediated dilatation.[76] Quercetin was administered to 12 hypertensive men at an oral dose of 1095 mg with reduction in BP by 7/3 mm Hg.[76] Forty-one prehypertensive and stage I hypertensive patients were enrolled in a randomized, double-blind, placebo-controlled, crossover study with 730 mg of quercetin per day vs placebo.[77] In stage I hypertensive patients, BP was reduced by 7/5 mm Hg (P<.05).[77] Quercetin administered to 93 overweight or obese patients at 150 mg/d during 6 weeks lowered SBP by 2.9 mm Hg in the hypertensive group and up to 3.7 mm Hg in patients aged 25 to 50 years.[78] The recommended dose of quercetin is 500 mg twice a day.

CLINICAL CONSIDERATIONS

Combining Food and Nutrients With Medications

Several of the strategic combinations of nutraceutical supplements together or with antihypertensive drugs have been shown to lower BP more than medication alone:

- Sesame with β-blockers, diuretics, and nifedipine
- Pycnogenol with ACE inhibitors and CCBs
- Lycopene with ACE inhibitors, CCBs, and diuretics
- Alpha lipoic acid with ACE inhibitors or acetyl-L-carnitine
- Vitamin C with CCBs

- N-acetyl cysteine with arginine
- Garlic with ACE inhibitors, diuretics, and β-blockers
- Coenzyme Q10 with ACE inhibitors and CCBs
- Taurine with magnesium
- Potassium with all antihypertensive agents
- Magnesium with all antihypertensive agents

Many antihypertensive drugs may cause nutrient depletions that can actually interfere with their antihypertensive action or cause other metabolic adverse effects manifested through the laboratory or with clinical symptoms.[79,80] Diuretics decrease potassium, magnesium, phosphorous, sodium, chloride, folate, vitamin B6, zinc, iodine, and coenzyme Q10; increase homocysteine, calcium, and creatinine; and elevate serum glucose by inducing insulin resistance. β-Blockers reduce coenzyme Q10. ACE inhibitors and ARBs reduce zinc.

CONCLUSIONS

Vascular biology such as endothelial and vascular smooth muscle dysfunction plays a primary role in the initiation and perpetuation of hypertension, cardiovascular disease, and target organ damage. Nutrient-gene interactions and epigenetics are a predominant factor in promoting beneficial or detrimental effects in cardiovascular health and hypertension. Food and nutrients can prevent, control, and treat hypertension through numerous vascular biology mechanisms. Oxidative stress, inflammation, and autoimmune dysfunction initiate and propagate hypertension and cardiovascular disease. There is a role for the select use of single and component nutraceutical supplements, vitamins, antioxidants, and minerals in the treatment of hypertension based on scientifically controlled studies as a complement to optimal nutritional, dietary intake from food, and other lifestyle modifications.[81] A clinical approach that incorporates diet, foods, nutrients, exercise, weight reduction, smoking cessation, alcohol and caffeine restriction, and other lifestyle strategies can be systematically and successfully incorporated into clinical practice (Table).

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