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Original article

Towards improved pharmacotherapy in pulmonary arterial hypertension. Can diet play a role?

Khrystyna O. Semen [a, b, *], Aalt Bast [a, c]

[a] Campus Venlo, Maastricht University, P.O. Box 8, 5900 AA, Venlo, the Netherlands
[b] Department of Propaedeutic of Internal Medicine #2, Danylo Halytsky Lviv National Medical University, Pekarska 69, 79010, Lviv, Ukraine
[c] Department of Pharmacology and Toxicology, Maastricht University, Faculty of Health, Medicine and Life Sciences, Maastricht, the Netherlands

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SUMMARY

Background: Pulmonary arterial hypertension (PAH) is a rare, progressive disease of the pulmonary vasculature. Recent advances in pharmacotherapy improved life expectancy of PAH patients and, thus, signified the role of general measures, including diet, in the management of the disease.
Methods: In the present narrative review we will briefly summarize information about current and novel PAH therapies and analyze preclinical evidence on the influence of certain nutrients on the pathogenesis of PAH.
Results: Although the evidence on the role of dietary deficiencies in the development and progression of PAH in humans is limited, preclinical studies demonstrate that dietary components such as quercetin, genistein, n-3 PUFAs, vitamin D, coenzyme Q10 and resveratrol may influence various aspects of PAH pathobiology.
Conclusions: Further research on the role of diet in PAH is needed. Taking into account pleiotropic and subtle effects of dietary constituents as well as the rare and severe nature of PAH, clinical studies on the disease-specific nutritional patterns rather than on single dietary components may help to reveal if diet can be an important tool to improve the efficacy of pharmacotherapy in PAH.

1. Introduction

Pulmonary arterial hypertension (PAH) is a chronic disorder of the pulmonary circulation, which is characterized by the progressive remodeling of the small arterioles, followed by an increase in pulmonary vascular resistance, right heart failure and death [1]. PAH is diagnosed as a sporadic (idiopathic PAH) or as a hereditary (heritable PAH) disease. It can also be associated with certain clinical conditions such as systemic sclerosis, human immunodeficiency virus (HIV) infection, portal hypertension, congenital heart disease, schistosomiasis or can develop after exposure to some drugs or toxins (Table 1) [1]. The estimated incidence and prevalence of PAH range from 2.4 to 10.7 and from 5 to 52 adults per million of adult population respectively [2–4]. Over the past 20 years PAH turned from a rapidly progressive fatal illness into a chronic disease with a relatively maintained quality of life but still with suboptimal prognosis with a 5-year survival rate of 61.2% in the newly-diagnosed cases [5,6].

Major advances in the management of PAH were related to use of the monotherapy targeting either endothelin, or prostacyclin or nitric oxide pathways [1]. Current evidence signifies multifactorial nature of the disease and gives substantial grounds to the multitargeted approach to its treatment. In fact, the benefits of the combination therapy with several PAH-specific drugs over monotherapy have been shown in recent clinical trials [7,8]. Even further, since the approved drugs act predominantly as vasodilators, the need to develop disease-modifying strategies has been postulated [9]. Nowadays, clinical trials exploring new therapeutic modulation of various disease-related pathways are underway [10–17] but is remains a long way to clarify which therapy will offer better chances for survival.

With PAH regarded as chronic treatable disease more emphasis has been laid on general supportive measures, including nutrition. In practice, nutritional counseling of the PAH patient frequently involves recommendations on water and sodium restriction and

* Corresponding author. Maastricht University, Campus Venlo, P.O. Box 8, 5900 AA Venlo, the Netherlands.
E-mail addresses: k.semen@maastrichtuniversity.nl (K.O. Semen), a.bast@maastrichtuniversity.nl (A. Bast).

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Table 1
Classification of pulmonary arterial hypertension.

I. Pulmonary arterial hypertension
1. Idiopathic
2. Heritable:
2.1. BMPR2 mutation
2.2. Other mutations
3. Drugs and toxins induced
4. Associated with:
4.1. Connective tissue disease
4.2. HIV infection
4.3. Portal hypertension
4.4. Congenial heart disease
4.5. Schistosomiasis
I'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
I''. Persistent pulmonary hypertension of the newborn

Note: BMPR2 – bone morphogenetic receptor 2; HIV – human immunodeficiency virus.

careful attitude to foods that are known to modify the cytochrome P450 pathway and, thereby, influence the efficacy of PAH-specific drugs. Recently, the concern has been raised about the impairment of the nutritional status in PAH [18,19]. Development of nutritional deficiencies in PAH can be caused by the potential role of increased energy demands, enhanced protein catabolism, congestion of the splanchnic organs related to the right-sided heart failure [19] as well as various metabolic derangements involved in PAH pathogenesis [18]. At the same time, evidence suggesting nutritional deficiencies in this disease is very limited.

Current understanding of the therapeutic potential of diet in the management of chronic disease goes far beyond the "deficiency correction" approach. By definition nutrition is a combination of many dietary components which act on a wide variety of targets and subtly modulate a multitude of physiological and pathological processes [20]. The effects of nutrition are chronic and not immediately evident [21] whereas dietary patterns and dietary ingredients are regarded as an essential modifiable lifestyle factors in prevention of many chronic respiratory and cardiovascular diseases [22–25].

Beneficial influence of certain nutritional components on the pathobiology of PAH has been supported by evidence from multiple preclinical studies. It can be foreseen that confirmation of those findings in human trials will be a major challenge due to rather small effect size as well as rareness and severity of the disease itself. Dietary choices may influence the course of the poorly treatable disease and potentiate the effects of drug therapy. In the present review we, therefore, will summarize information about current and novel PAH therapies and analyze preclinical evidence on the influence of certain nutrients on the pathogenesis of PAH. The question whether diet can be regarded as an important tool to improve the efficacy of pharmacotherapy in PAH will be discussed.

2. Current therapy for PAH

Current therapeutic armamentarium for PAH targets three main pathogenic pathways and includes 12 approved medications, which were demonstrated to improve the symptoms, exercise tolerance, hemodynamics or to increase the time to clinical worsening (Table 2) [1,26].

The role of endothelial dysfunction and impaired NO metabolism, which lead to increased pulmonary vasomotor tone and remodeling of pulmonary arteries has been well characterized in the pathogenesis of PAH [27–29]. Low levels of NO plasma metabolites have been related to changes in pulmonary hemodynamics and even mortality in patients with idiopathic PAH [30].

NO is a low molecular-weight free radical, which exerts it's vasodilatory action through binding to soluble guanylyl cyclase (sGC) with subsequent stimulation of cyclic guanosine monophosphate (cGMP) synthesis, activation of protein kinase G and decrease in the cytosolic Ca^{2+} concentration [31]. NO also interacts directly with 1) protein kinases and phosphatases changing their activity 2) lipids and 3) hemoproteins or 4) takes part in free radical reactions. In pulmonary vasculature NO is produced by endothelial NO synthases (eNOS), which, in the presence of oxygen, NADPH and other cofactors, catalyzes the oxidation of L-arginine to L-citrulline. Moreover, it can be derived from diet or be resynthesized trough enterosalivary nitrate-nitrite-NO pathways [28,32,33].

The drugs used for treatment of PAH potentiate the effects of NO in several ways; (i) by preventing breakdown of cGMP through inhibition of its hydrolysis by phosphodiesterase type 5 (*PDE-5 inhibitors* - sildenafil, tadalafil); (ii) by stimulation of sGC (sGC *stimulators* - riociguat); (iii) by NO replacement (inhaled NO is used for persistent pulmonary hypertension in newborn). The major effects of therapeutic manipulation on the NO/cGMP pathway in PAH include vasodilation, anti-proliferation and induction of apoptosis [34,35].

The other pathway which is therapeutically deployed in PAH involves prostacyclin-thromboxane A2. Prostacyclin or prostaglandin I_2 (PGI_2) is not only a potent vasodilator in the pulmonary arteries but it also has antithrombotic, antiproliferative, antimitogenic, anti-inflammatory properties. PGI_2 is produced from arachidonic acid via cyclooxygenase and prostacyclin synthase and acts on the specific I-prostanoid (IP) receptors which are largely expressed on vascular smooth muscle cells (VSMC). Upon activation IP receptors, accumulation of cyclic adenosine monophosphate (cAMP) occurs, which increases activity of protein kinase A (PKA) and promotes a PGI_2 effects [36]. The drugs designed to potentiate PGI_2 signaling in PAH act either by restoring PGI_2 deficit (prostacyclin analogs – epoprostenol, iloprost, treprostinil, beraprost) or by stimulating IP receptors (selexipag) [37]. Recent studies demonstrated that activation of peroxisome proliferator-activated receptors – β/δ is involved in the rapid vasodilatory effect of prostacyclin analogs [38].

Finally, upregulation of the endothelin-1 (ET-1) pathway is associated with vasoconstriction and increased proliferation of VSMC in the pulmonary circulation [39]. Effects of ET-1 are realized through two G protein-coupled ET-1 receptor subtypes: endothelin receptor A (ET_AR) and endothelin receptor B (ET_BR). Action of ET-1 on both receptors expressed in VSMC stimulates vasoconstriction and proliferation, while activation of ET_BR on endothelial cells promotes relaxation of the vessels through increased production of prostaglandin I_2 (PGI_2) and NO [40]. ET-1-mediated responses in PAH are limited by administration of endothelin receptor antagonists, which cause dual (bosentan and macitentan) or selective (ET_AR – ambrisentan) blockade of ET-1 receptors [1].

It is not clear what affects individual responses to specific treatment in PAH and literature lacks comparative clinical trials to substantiate initial and specific selection of drugs. Empirically, oral therapy is preferred in the early and moderate stages of the disease while parenteral drugs are commonly used in advanced stages [1]. Combination therapy in PAH has an obvious potential when the complexity of disease pathogenesis is taken into account. A sequential combination therapy approach, which requires introducing one drug on top of the other whenever an optimal therapeutic response could be reached with initial monotherapy, was introduced by expert consensus in 2009 [41]. Recently the concept of first-line combination therapy received more attention [7]. In fact, current achievements in PAH management with the increase in the life span and improvement of the life quality can be largely attributed to combination therapy as the majority of the patients had more than one medication prescribed.

Table 2
Approved and emerging therapies in the management of PAH.

Approved therapies			
Prostacyclin pathway	Prostacyclin analogs: • Epoprostenol • Iloprost • Treprostinil • Beraprost	Prostacyclin receptor agonists: • Selexipag	
Nitric oxide pathway	Phosphodiesterase type-5 inhibitors: • Sildenafil • Tadalafil • Vardenafil	Soluble guanylate cyclase stimulators: • Riociguat	NO: • inhaled NO
Endothelin pathway	Endothelin receptor antagonists: • Ambrisentan • Bosentan • Macitenan		
Emerging therapies			
Target mitochondrial and metabolic dysfunction: • Dichloroacetate • Bardoxolone methyl • Ranolazine • Trimetazidine		Reduce inflammatory/immune dysfunction: • Rituximab • Tocilizumab • Ubenimex • Anakinra	
Restore BMPR2 signaling: • Tacrolimus		Correct iron deficiency: • Ferinject	
Improve right ventricular function: • Carvedilol			

2.1. Novel approaches to management of PAH

Despite major advances in treatment of PAH the patients still show signs of the disease progression [42] and lung transplantation is regarded as the only curative therapy. Obliterate remodeling in the pulmonary vasculature, fibrotic changes, as well as signs of perivascular and interstitial inflammation are only partially reduced by PAH specific drugs, as it was shown by comprehensive pathology examination of lung explants from systematically treated PAH patients [43]. Disappointing lessons have been learned from attempts to control excessive cell proliferation with tyrosine kinase inhibitors, statins and serotonin antagonists [44].

Currently several drugs are investigated in phase II clinical trials (Table 2). They may be categorized into those that target mitochondrial and metabolic dysfunction (dichloroacetate, bardoxolone methyl, ranolazine, trimetazidine), restore BMPR2 signaling (tacrolimus), reduce inflammatory/immune dysfunction (rituximab, tocilizumab, ubenimex, anakinra), correct iron deficiency (ferinject) and improve right ventricular dysfunction (carvedilol) [11,12,14,45–47]. The multitude of the possible therapeutic targets presents challenges for patient recruitment. Moreover, it is not completely clear which interventions will yield more control of the PAH pathobiology. It seems that at the present state of things potentiation of the effects of the approved therapies, which already influence many aspects of the disease pathogenesis, by nutritional components may further contribute to improvement of treatment outcomes.

3. Diet as a tool to enhance the effects of the existing therapies

By definition nutrition is a combination of many dietary components which act on a wide variety of targets and subtly modulate a multitude of physiological processes [20]. Nowadays dietary interventions evolved into a recognized player in the field of preventive medicine with documented causal relationships between the nutritional pattern and risk of major chronic diseases and cancer [48–50]. At the same time, diet is regarded as a lifestyle factor modifying various cardiovascular and respiratory diseases [51,52]. In contrast to drug therapy, which frequently gives significant effects and requires large-scale randomized clinical trials for regulatory approval, the effects of the nutritional interventions are chronic, not immediately evident and ways to evaluate their action are still debated [21] Therefore, providing evidence for nutritional recommendations in severe rare disorders, like PAH, is extremely challenging. At the same time, it can be also anticipated that beneficial action of the dietary constituents towards inflammation, endothelial dysfunction or oxidative stress, shown in various multifactorial disorders [53–56] can be applied in PAH, particularly, to potentiate the action of existing specific therapy (Fig. 1). More comprehensive dietary counseling based on the evidence from other chronic disease with a comparable pathophysiology will help patients to become more “in charge of their own illness”. Additionally, that can be also regarded as an important part of an individual psychological management of the disease.

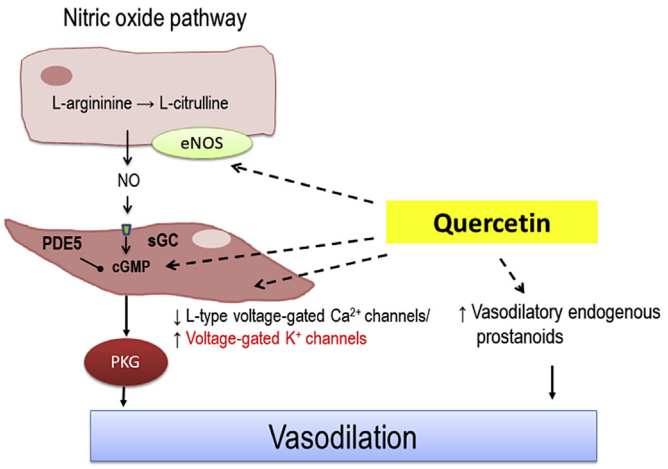

Fig. 1. Mechanisms of vasodilatory action of quercetin. Quercetin can produce vasodilation via several pathways. Except of influencing the activity of eNOS, it was demonstrated to increase the concentration of cGMP in endothelium-independent manner, change the activity of voltage-gated K^+ and Ca^{2+} channels, and increase the level of vasodilatory endogenous prostanoids. eNOS - endothelium nitric oxide synthase, PDE5 – phosphodiesterase type 5, PKG – protein kinase G, sCG – soluble guanylyl cyclase; cGMP – cyclic guanosine monophosphate.

4. Role of nutritional deficiencies in PAH

The evidence on the relationships between deficiencies of certain nutrients and PAH is rather limited. Most of the cases describe PAH developing secondary to a certain micronutrient disease than *vice versa*.

Severe pulmonary hypertension due to the inborn error of vitamin B12 metabolism (cobalamin C disease), linked in some cases to the presence of a homozygous mutation in the MMACHC gene, has been reported in several observations [57–59]. Moreover, deficiency of vitamin C and iron [60] were linked to development of reversible pulmonary hypertension. The role of the vitamin deficiency in the development of PAH was further elucidated in a study involving 115 subjects from cardiology and infectious disease outpatient clinic demonstrating very low levels of vitamin D [61]. Comparing to the control group those individuals showed increased systolic pressure in the pulmonary artery (sPAP) evaluated by echocardiography. The authors speculate that this effect may be caused by hyperparathyroidism related to deficiency of vitamin D [61]. In a small study by Tanaka et al., [62], low serum levels of 25-hydroxyvitamin D [25(OH)D] were demonstrated in 12 patients with idiopathic PAH. Furthermore, idiopathic PAH patients ($n = 8$) were found to have low plasma levels of the active metabolite of vitamin A, all-*trans* retinoic acid. This deficiency was suggested to contribute to the increased proliferative potential of VSMC in the pulmonary vasculature [63]. In the same study low levels of α-tocopherol and β-carotene were reported [63]. Severe reversible pulmonary hypertension was diagnosed in a clinical case of multiple vitamin deficiency involving vitamin C, thiamine (vitamin B1), pyridoxine (vitamin B6), cobalamin (vitamin B12), and vitamin D [64]. Finally, single oral administration of niacin (vitamin B3), which is known to induce release of vasodilatory prostaglandins acting on the pulmonary circulation, failed to reduce elevated tricuspid regurgitation jet velocity (a surrogate for sPAP) in subjects without previous known pulmonary vascular disease [65].

The relationship between PAH and general nutritional status has been also addressed. In a cohort involving 179 hemodialysis patients malnutrition, low levels of total cholesterol, triglycerides and albumin were identified as risk factors for the development of pulmonary hypertension [66]. On the contrary, in the study of Kawamoto et al. presence of cachexia in the pulmonary hypertension patients has been linked to RV function, degree of PAP elevation and low cardiac output [19]. Authors conclude that the nutritional status may be a surrogate marker of the severity of the PAH and point to the reported reversibility of the nutritional deficiencies after lung transplantation [67].

Thus, evidence on the role of the nutritional status in the development and progression of PAH is limited. With exception of the severe vitamin deficiencies cases, it is largely unclear whether interventions targeting nutritional status in general would improve PAH or its prognosis.

5. Beneficial effects of certain nutrients in PAH

The action of several food derived components on various aspects of PAH pathobiology was evaluated in experimental studies. Improvement of the pulmonary hemodynamics and remodeling of the pulmonary arteries was demonstrated in the monocrotaline and hypoxic model of PAH for dietary polyphenols, viz. quercetin [68–70], rutin [71], grape seed procyanidin extract [72], genistein [73,74], baicalin [75,76], and also compounds like folic acid [77], resveratrol [78–83] and co-enzyme Q10 [84]. n-3 Polyunsaturated fatty acids (n-3 PUFA) have been shown to reduce inflammation and proliferation of pulmonary artery smooth muscle cells [85]. Moreover, n-3 PUFAs exhibited potent vasodilatory action on lamb fetal [86], sheep [87] and murine [88] pulmonary arteries in various models of pulmonary hypertension.

Demonstrated efficacy towards different aspects of the PAH pathobiology for the several dietary compounds may substantiate their potential for the application in human. More details on the specific nutrients studied in PAH are provided below.

5.1. Quercetin

Quercetin is one of the most abundant natural flavonoids present in the human diet. It has been noted with a wide spectrum of biological effects, which include modulation of the redox processes, inflammation, immune response, as well as antiaging and anticancer activity [89,90]. Protective action of quercetin in respiratory disorders was underscored by its feature to accumulate in the lung [91]. Robust data on the mechanisms of action of quercetin supported its use in pulmonary hypertension models.

The vasodilatory action of quercetin has primarily been described in systemic circulation vessels in organ-bath experiments [92]. Its influence of the diseased pulmonary circulation were studied in monocrotaline (MCT) and hypoxic models of pulmonary hypertension. Supplementation with quercetin in a preventive (100 mg kg^{-1} from the day after MCT injection) and therapeutic manner (10 mg kg^{-1} once daily from day 21 when pulmonary hypertension was established) to MCT rats lowered pulmonary arterial pressure, inhibited right ventricular hypertrophy and muscularization of the pulmonary arteries [68,70]. In isolated pulmonary arteries from MCT-treated rats quercetin induced vasodilation after stimulation with thromboxane A_2 mimetic U46619 [68]. A similar protective effect of quercetin on pulmonary vasculature was observed in a chronic hypoxia model of pulmonary hypertension [69,93,94]. The endothelium-dependent and endothelium-independent mechanisms (Fig. 2) were shown to be involved in quercetin-induced vasodilation [95–100].

Several PAH animal model studies demonstrated antiproliferative action of quercetin. Given in a preventive mode (100 mg/(kg·d) from the next day after MCT injection throughout the period of model development) quercetin reduced wall thickness of pulmonary arteries and alleviated expression of the proliferating cell nuclear potential antigen in the pulmonary artery smooth muscle cells (PASMC) from MCT treated rats [70]. Antiproliferative and pro-apoptotic effects of quercetin were further confirmed by decreased muscularization of the small pulmonary arteries and inhibition of 5-bromo-2′-deoxyuridine (BrdU) and/or 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyltetrazolium bromide incorporation in PASMC and fibroblasts from MCT rats [68]. Modulation of Akt signaling and FOXO1 dependent pathways were suggested to be responsible for the antiproliferative effect of quercetin [68,69,93]. This effect may be particularly valuable since upregulated expression of Akt and Erk1/2 is well known to be involved in the trans differentiation of pulmonary endothelial cells into smooth muscle-like cells – a typical abnormality observed in PAH [101].

Similarly to the conventional PAH-specific therapy, quercetin was shown to counteract effects of endothelin 1 [102] and to improve bioavailability of NO (reviewed in [103]). Moreover, oral administration of quercetin in human did not show any adverse effects in the dose up to 730 mg per day during one month [104,105]. Recently, the concern was raised about the possibility of quercetin to interfere with iron metabolism [106]. The extent to which these arguments are applicable in PAH warrants further study.

5.2. Resveratrol

Resveratrol (3,5,4-trihydroxystilbene) is a natural polyphenol found in many plants including red grapes and berries. It has

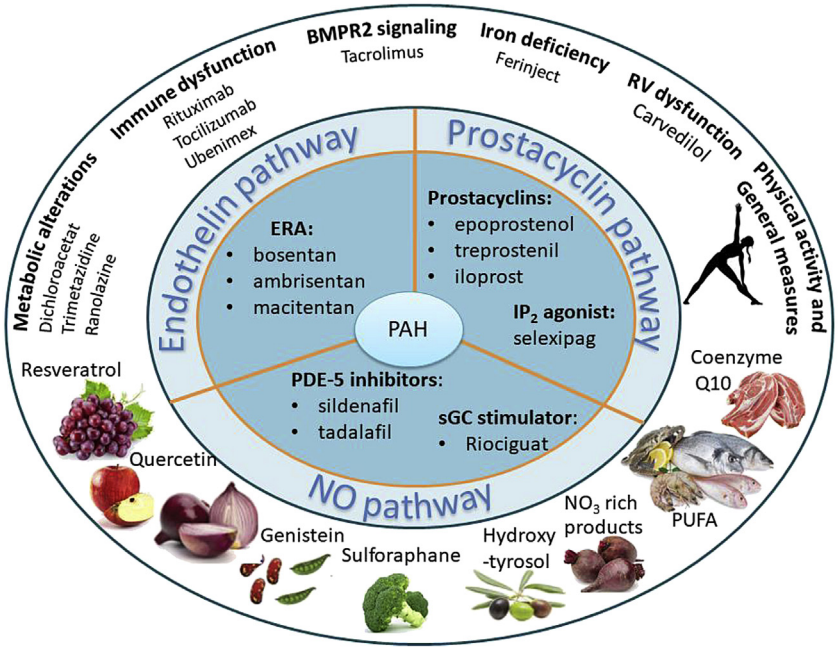

Fig. 2. Overview of the therapeutic modalities of PAH: role of nutrition. The center of the figure presents three major therapeutic strategies currently involved in management of PAH. New compounds (outer circle) that show promise in the preclinical studies, are currently tested in phase 2-3 clinical trials. The role of physical activity based rehabilitation programs and optimal general supportive measures are increasingly recognized as important part in PAH treatment. Accumulating evidence from the preclinical studies shows that dietary constituents may act on the targets relevant to PAH pathogenesis and, therefore, may be expected to offer benefit in the general management of this disease. BMPR2 - bone morphogenetic protein receptor type 2; ERA – endothelin receptor antagonists, IP2 – prostanoid 2; NO – nitric oxide; PAH – pulmonary arterial hypertension; PDE-phosphodiesterase, PUFA – polyunsaturated fatty acids; RV – right ventricular; sGC – soluble guanylyl cyclase.

antioxidant, anti-inflammatory, anti-proliferative, anti-fibrotic and endothelial protective effects in the systemic circulations [107]. The influence of resveratrol in PAH has been studied in MCT and hypoxic models. The first study published by Csiszar et al., showed reduction of the pulmonary VSMC proliferation and improvement of the indexes of pulmonary hemodynamics in MCT rats [81]. Subsequently, positive effects of resveratrol on MCT-induced pathomorphological changes and pulmonary hemodynamics were confirmed by other researchers using this polyphenol either in a preventive [78] or therapeutic [82] manner. Reversal of pulmonary arterial remodeling and lowering of right ventricular systolic pressure were also confirmed in the hypoxic model of pulmonary hypertension [108]. Besides influence on the small pulmonary arteries resveratrol also reduced media hypertrophy in the pulmonary trunk [79].

Upregulation of silence information regulator 1 (SIRT1), a cellular factor involved in the control of angiogenesis, vascular tone and endothelial function, was suggested to be responsible for the anti-proliferative action of resveratrol [78]. Activation of SIRT1 with subsequent normalization of the atrophic ubiquitin ligase atroglin-1 was shown to play a role in resveratrol-induced inhibition of VSMC hypertrophy and proliferation in the MCT model [82]. Also in the hypoxic model, resveratrol enhanced activation of SIRT1, thus, inhibiting PASMC proliferation and promoting their apoptosis [109]. Other effects of resveratrol in the hypoxic pulmonary hypertension model include reduction of oxidative stress and inflammation, which were attributed to inhibition of HIF-1 signaling *via* suppression of the MAPK/ERK1 and PI3K/AKT pathways and restoration of the activity of the nuclear factor erythroid-2 related factor 2/thioredoxine 1 antioxidant axis [108].

In human PASMC resveratrol abrogated hypoxia-induced cell proliferation and attenuated hypoxic induction of arginase II, the mitochondrial isoform of the enzyme arginase [80]. Interestingly, in patients with PAH, arginase activity and expression are elevated in the serum and vascular wall of the pulmonary arteries, respectively [110]. Targeting arginase has been mentioned as of the promising therapeutic approaches in PAH [111]. The effect of resveratrol upon arginase II occurs via inhibition of the PI3K-Akt signaling pathway, which is consistent with the evidence on the role of Akt signaling in cellular proliferation, particularly with regards to PASMC [112,113].

Except for its anti-proliferative potential, resveratrol was also shown to improve endothelial dysfunction by increasing eNOS expression and bioavailability of NO [81,108]. The vasodilatory action of resveratrol was confirmed by flow mediated dilation study, demonstrating a more prominent effect comparing to other vasoactive nutrients, such as cocoa flavanols, tea catechin, epigallocatechin gallate and soy isoflavones [114].

Right ventricular (RV) dysfunction is an important factor determining the course of the disease [42]. Together with improvement of the pulmonary hemodynamics resveratrol was shown to decrease indexes of RV hypertrophy and to reduce hypertrophy and apoptosis of cardiac myocytes [81,108,115]. These effects were not observed in the study by Wilson et al., [79], which might be explained by differences in dosing and frequencies of resveratrol use (25 mg/kg/day versus 10-40 mg/kg twice a day in other series).

Thus, accumulating experimental evidence suggests anti-proliferative, vasodilatory, anti-inflammatory and antioxidant effects of resveratrol in PAH-like pulmonary circulation. Clinical trials in various fields found this polyphenol to be safe and reasonably well tolerated [116]. One of the important implication for its use in PAH concerns its inhibitory action on the cytochrome P450 isoenzymes [117], which can contribute to an increase in the plasma concentration of sildenafil [1]. Combination of resveratrol and sildenafil may potentiate control over endothelial dysfunction, as it was shown in the study on diabetic erectile dysfunction [118].

5.3. Hydroxytyrosol

Extra virgin olive oil, an essential component of the Mediterranean diet, has antioxidant, anti-inflammatory, vasodilatory, and antiplatelet properties [119,120]. Its main cardio- and vascular protective effect were attributed to the presence of phenolic compounds, in particular hydroxytyrosol (3,4 dihydroxyphenylethanol, HT), which improves signs of endothelial dysfunction and promotes vasodilation [121,122]. To ensure the protective effect of HT on the atherosclerosis and cardiovascular health the daily intake of 5 mg of HT or its derivatives has been recommended by European Food Safety Authority, which is equivalent to at least 20 g of extra virgin olive oil [120,123]. This health claim might be applicable also to PAH patients, where endothelial dysfunction as well as formation of the atherosclerotic plaques in the pulmonary arteries during the advancement of the disease are well-recognized abnormalities.

5.4. Genistein

Another dietary component with a beneficial effect on pulmonary circulation is genistein. Derived from soy beans, this phytoestrogen has been shown to attenuate development of pulmonary hypertension and to reverse preexisting established disease in MCT and hypoxic PAH models [73,74,124,125]. Similarly to other polyphenols, genistein improved cardiopulmonary structure and function in animal models of PAH and inhibited proliferation of human PASMC *in vitro* [73,126]. Suppression of microRNA206 and restoration of the pulmonary hypertension-induced downregulation of estrogen receptor-β expression in the right ventricle and lung were suggested as the putative mechanisms involved in the protective effects of genistein in the model studies [73,126]. However, the later action of genistein may raise concerns because of the possible involvement of estrogen signaling in the pathobiology of PAH [127]. At the same time, no uniform hazardous influence of this sex hormone in PAH has been reported. Complexity of the estrogen processing pathways with counteracting effects of various metabolites on the pulmonary circulation [127] and paradoxical worse disease outcomes in male [128] are important arguments to question causative role of estrogens in development of PAH. Low affinity of genistein to cytoplasmic and nuclear estrogen receptors with its binding affinity of about 100–1000 times less than that of estrogen [129] also reduces the likelihood of the adverse events related to this phytoestrogen.

Further suggestions about the therapeutic potential of genistein in PAH are supported by evidence on its ability to improve bioavailability of NO and stimulate expression of eNOS [74,124,125,130,131]. Moreover, stimulation of endothelium-independent vasodilation was described in the isolated porcine coronary arteries [132]. In addition to prominent vasodilatory effects, genistein has been implied to control excessive cell proliferation typical of cancer [133] and PAH. Genistein was reported with synergistic behavior with well-known anticancer drugs, such as adriamycin, docetaxel, and tamoxifen [133]. An add-on effect of genistein with various PAH specific medications may be expected.

5.5. Coenzyme Q

Coenzyme Q10 (CoQ10) has shown promising potential in the prevention and treatment of cardiovascular disease [134]. CoQ10 is known to be of importance for the mitochondrial metabolism due to its electron carrier function as well as for its redox cycling antioxidants properties. The dietary products rich in CoQ10 include organ meat, spinach, broccoli, cauliflower, and legumes such as peanuts and soybeans. As the role of mitochondrial dysfunction in the pathobiology of PAH has been increasingly acknowledged [11], more attention is being paid to this compound. The results of a small scale clinical trial involving supplementation with CoQ10 showed improvement in hemoglobin and red blood cell maturation in PAH patients [84]. Recently, in a clinical case relating mitochondrial dysfunction with pulmonary hypertension the benefit of therapy involving CoQ10 has been described [135]. Good safety profile of CoQ10 has been supported by evidence from the studies involving patients with heart failure [136].

The effects of CoQ10 may be potentiated by its combination with the other nutrients. A preclinical study involving endothelial cells and cardiomyocytes from an animal model showed better effects of CoQ10 when combined with vitamin D3 and L-arginine on the NO production and vasodilation compared to the action of each nutrient alone [137]. It can be assumed that consumption of CoQ10 in a food matrix, rich in antioxidants and compounds acting on the NO pathway may offer some benefit in cases of dysfunctional NO signaling.

5.6. Polyunsaturated fatty acids

The vasodilatory action of n-3 PUFAs on the pulmonary vasculature is well documented [86,87,138]. Eicosapentanoic acid (EPA) was shown to produce vasorelaxation in the pulmonary artery by 1) increased production of NO (endothelium-dependent mechanism); 2) increased production of vasodilatory prostaglandin I_3; and 3) inhibition of the Ca^{2+} influx through the L-type calcium channels and reduced release of Ca^{2+} from intracellular stores [87]. The endothelium-dependent vasorelaxation by EPA involves modulation of the lipid composition of the caveolae of the endothelial cells, which promotes migration of caveolae-bound eNOS to the cytoplasm and activates eNOS [139]. More recently, activation of eNOS with EPA supplementation was attributed to upregulation of the redox sensitive PI3-kinase/Akt and MAPK pathways [138]. Thus, EPA reverses endothelial dysfunction and improves production of nitric oxide both due to direct modulatory effect on the membranes and stimulation of redox sensitive pathways.

Modulation of the membrane channels activity is another mechanisms of the vasodilatory action of n-3 PUFAs. A major metabolite of n-3 PUFAs produced via CYP450 epoxygenase pathway 17(18)-epoxyeicosatetranoic acid was also shown to induce concentration-dependent relaxation of human pulmonary arteries through activation of calcium-dependent potassium channels (BK_{Ca}) [140]. That was confirmed in another study where the vasodilatory effects of infusion of n-3 PUFAs in the fetal pulmonary circulation was blocked by inhibitors of potassium channels and CYP450 epoxygenase [86].

Except from the effect on BK_{Ca} channels, PUFAs also act upon two-pore domain potassium channels (K_{2P}) which are involved in hyperpolarization of the cell membrane that leads to closure of voltage-gated Ca^{2+} channels and thereby vasorelaxation [88]. The family of K_{2P} channels have been implicated in the regulation of pulmonary vascular resistance and possible development of pulmonary hypertension [88,141,142]. Lipid dependence was reported for another family of K^+ channels, voltage-activated K^+(Kv) channels, which are responsible for setting the membrane potential of the pulmonary artery smooth muscle cells [143]. Interaction of PUFAs with the plasma membrane channels involved into pathobiology of PAH may promote vasodilation and, thus, beneficially affects the course of the disease.

Except for acting on the vascular tone, both EPA, docosahexanoic acid (DHA) and their intermediary docosapentanoic acid (DPA, 22:5 n-3) were shown to reduce production of the proinflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α) [85,144] and promote synthesis of pro-resolving lipid mediators [145]. Dietary supplementation with n-3 PUFAs stimulated conversion of EPA and DHA into

bioactive metabolites such as resolvins and protectins, which contribute to reduction of chronic inflammation [146]. Monoacylglyceride of DPA was shown to inhibit upregulation of the NFkB pathway and to fine-tune the transcription process which plays a role in modulation of pulmonary artery inflammation and remodeling typical of PAH [85]. A beneficial effect of PUFAs may be also attributed to the activation of peroxisome proliferator-activated receptor γ (PPARγ) [147], which is expressed abundantly in pulmonary vascular endothelial cells in normal human lung, but not in the vascular lesions of rats with pulmonary hypertension or in plexiform lesions in the human lungs [148]. Stimulation of PPARγ reduced pulmonary vascular vasoconstriction, inflammation and remodeling in experimental models of pulmonary hypertension [149–151].

It should be noted that the rate of production of EPA and DHA in the human body is extremely slow. Relative deficiency of n-3 fatty acids was shown in a small cohort of newly-diagnosed PAH patients [152]. Thus, dietary supplementation with n-3 PUFA may help to restore n-6/n-3 balance in this population and possibly promote vasodilatory, anti-inflammatory and anti-proliferative effects of the specific drugs. Further investigations confirming this assumption are required.

5.7. Vitamin D

As mentioned previously, deficiency of vitamin D have been associated with increase in systolic pulmonary arterial pressure [61] and *vice versa* patients with diagnosed PAH were found with a reduced levels of serum 25(OH)D [62]. A small clinical study involving 22 patients with pulmonary hypertension and vitamin D deficiency investigated the effects of cholecalciferol administered together with zinc and magnesium for 3 months [153]. Combined administration of those nutrients resulted in increase of the distance in the 6-min walk test and reduced dimensions of RV without major improvement in the pulmonary hemodynamics [153]. Small sample size, short observation period as well as use of combined intervention make results of this study difficult to interpret in terms of the potential role of the vitamin D deficiency PAH.

At the same time, beneficial influence of vitamin D on the indexes of right ventricular hypertrophy was further confirmed in the SU5416/hypoxia model of pulmonary hypertension [62]. The authors concluded that insufficient intake of vitamin D might potentially accelerate RV dysfunction [62].

Anti-proliferative and anti-inflammatory action of vitamin D can be assumed from *in vitro* studies. Vitamin D was shown to inhibit endothelin-induced proliferation of smooth muscle cells [154], to prevent profibrotic phenotype of lung fibroblasts and epithelial cells [155] and to improve NO bioavailability via upregulation of eNOS [156]. Reduction of the inflammatory response in monocytes and potentiation of their steroid sensitivity by vitamin D was also noted [157,158].

Undoubtedly, prevalence of the vitamin D deficiency in PAH patient as well as the value of its supplementation should be addressed in larger studies before any recommendation can be made. At the same time, it is justified to suggest paying attention to sufficient dietary intake of vitamin D as a part of general management plan in PAH.

5.8. Nitrate rich products

Nitrate-rich dietary products, such as green leafy vegetables, red beet, spinach, radish and celerycan were suggested to be involved in the beneficial modulation of cGMP-dependent signaling [32]. Oral supplementation with inorganic nitrate or nitrate-containing foods caused pleiotropic beneficial effects on pulmonary vasculature in the setting of inflammation, endothelial dysfunction, ischemia-reperfusion injury and in pre-clinical models of pulmonary hypertension [159]. An excellent review has been published recently implicating the role of the entero-salivary nitrate metabolism on the pulmonary vascular health [160].

Currently the result of the study evaluating efficacy of the short-term supplementation with the nitrate rich beetroot juice on the VO_{2max} are awaited (NCT02000856). Sufficient intake of the nitrate-rich dietary products can be encouraged to maintain optimal balance of NO. However, the extent to which such strategy may influence the course and outcomes in PAH needs to be clarified.

5.9. Activators of Nrf2

Activation of Nrf2 has been associated with prominent anti-inflammatory, antioxidant, antiproliferative and anticarcinogenic effects *in vitro* [161,162]. The results from SU5416/hypoxia model of pulmonary hypertension showed that upregulation of Nrf2 with protandim (a mixture of five plant derived ingredients) increased expression of genes encoding for antioxidant enzymes and protected against development of right heart failure [163]. In another study involving hypoxia-induced pulmonary hypertension, administration of the Nrf2 activator oltipraz to mice not only improved right ventricular hypertrophy but also reduced obliterative remodeling in pulmonary arteries [164]. Clinical trials evaluating effects of Nrf-2 activators triterpenoid bardoxolone methyl and dimethyl fumarate in PAH are currently underway [165,166] pointing out to recognized potential of Nrf2 activators in the management of PAH.

At the same time, certain dietary components are well known activators of Nrf2 and, therefore, may present a certain benefit in the management of PAH. For example, sulforaphane, a compound produced by the hydrolytic conversion of glucoraphanin after ingestion of cruciferous vegetables, particularly broccoli and broccoli sprouts has been shown to target excessive cellular proliferation via modulation of redox homeostasis and activation of the Keap1/Nrf2 pathway [167–169]. In smooth muscle cells, sulforaphane inhibited cell proliferation by targeting mTOR/p70S6kinase signaling [170]. Moreover, suppression of NFkB-mediated inflammatory response as well as anti-oxidant effects contributed to the improvement of endothelial function reported in the model studies with sulforaphane [171]. Significant anti-fibrotic effects of sulforaphane was noted in TGF-β-treated cell lines [172].

Dietary flavonoids represent another group of compounds acting upon the Keap1/Nrf2 pathway. A two-step mechanism was suggested to play a role. Initially, flavonoids act as antioxidants and per definition become oxidized. Secondly, the oxidized metabolites react with the thiol groups of Keap1, which causes activation of Nrf2 [173].

6. Limitation of the review and potential implication of diet in management of PAH

The major limitation of this review is the fact that evidence has been derived predominantly from preclinical models which approximate but do not completely mimic an actual disease. Low prevalence and still unfavorable course of PAH make organization of the clinical studies evaluating effects of one particular nutritional component rather difficult. At the same time it becomes increasingly debated that application of the traditional approached with randomized clinical trials may be not the most optimal way to estimate efficacy of the food constituents. That is because nutrients exhibit subtle multifaceted action over relatively long period of time rather than produce rapid, clinically significant changes expected of drugs. Moreover, over the past decades the focus of

nutritional science has moved from management of specific nutritional deficiencies to recognition of the role of the dietary patterns in chronic disease. Existing preclinical evidence can serve as the base for development of the such patterns for PAH.

Recent advances in the pharmacotherapy allowed to extend the life span of PAH patients. Nowadays, the disease is no longer considered as fatal but rather chronic with limited life expectancy. While the search for cure continues with preclinical and clinical studies, the patients await the tools to improve the quality of their lives. Dietary counseling with suggestions about beneficial dietary choices may be helpful in turning patients into more active participants in the management of their dreadful illness. Reasoning for efficacy and safety of such recommendations can be drawn from the experimental studies as well as by repurposing of the dietary approached applied in the more common disorders with a similar pathogenetic background.

7. Conclusions

Although PAH is regarded as a rare disease, it carries significant social and economic impact due to the relatively young age of the affected population and high costs of available therapies [174]. The evidence on the role of dietary deficiencies in the development and progression of the PAH is currently limited. At the same time, it can be assumed that a better and more careful diet in patients with PAH would improve both their quality of life and the drug safety. Multiple preclinical studies demonstrate that dietary components such as flavonoids, n-3 PUFAs, vitamin D, coenzyme Q10, resveratrol, etc., may influence various aspects of PAH pathobiology including endothelial dysfunction, arterial remodeling, inflammation, oxidative stress and disorders of microRNAs signaling. Evaluation of these effects in clinical trials would be the next step towards development of the specific nutritional recommendations. Taking into account pleiotropic and subtle effects of nutrition, clinical study on the disease-specific nutritional pattern rather than single dietary components may be the most efficient way to reveal if diet can be an important tool to improve the efficacy of pharmacotherapy in PAH.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2018.12.087.

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