Special Article

Nutraceutical for Autosomal Dominant Polycystic Kidney Disease Therapy

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder caused by mutations of either PKD1 or PKD2 gene. Cyst formation initiates from a combination of abnormal cell proliferation along with enhanced fluid secretion. ADPKD is characterized by the progressive enlargement of cysts which destroy the renal parenchymal cells, resulting in renal failure. Currently, there is no effective treatment for this disease. Interestingly, several relevant therapeutic effects of herbal medicine relevant to pathogenic process of ADPKD have urged the researchers to search for potential candidate herb as nutraceutical for ADPKD therapy. Up to now, several natural compounds, such as triptolide, curcumin, ginkolide B, and steviol (stevia extract) have been shown to be able to retard cyst progression in ADPKD. The detailed mechanism of these compounds showed that triptolide enhanced calcium restoration, curcumin inhibited ERK & p-STAT 3 pathways, ginkolide B inhibited Ras/MAPK pathway, and steviol activated AMPK, which inhibited CFTR channel and mTOR pathway in cell and mouse models of PKD. In addition, they are currently in preclinical and clinical studies, respectively. This review focuses on the pathophysiology of ADPKD and the recent therapeutic approaches, especially a potential use of nutraceutical for the treatment of autosomal dominant polycystic kidney disease.

Keywords: *ADPKD, Cyst growth, Natural compound, Therapeutic approaches*

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common form of PKD. It is inherited in an autosomal dominant pattern and caused by mutation of either *PKD1* or *PKD2* gene[1]. *PKD1* and *PKD2* genes encode polycystin 1 (PC1) and polycystin 2 (PC2) proteins, respectively. Mutation of *PKD1* gene accounts for 85% of cases and is more severe than the mutation of *PKD2* gene, which is responsible for only 15% of cases. ADPKD normally occurs in adulthood with an incidence of 1:400 to 1:1,000 live births[2]. The characteristic of ADPKD is the progression of cysts along the nephron. These numerous fluid-filled cysts are gradually enlarged and replaced renal parenchymal cells. ADPKD patients have a wide range of symptoms including hypertension, polyuria, back pain, kidney stone, and urinary tract infection[3,4]. These symptoms usually occur in adult at third and fourth decades of life, and progress to renal failure that require either dialysis or renal transplantation.

At present, advancement in the studies concerning the basic molecular biology of the disease has revealed that fluid-filled cysts in ADPKD are formed by abnormal cell proliferation and massive transepithelial fluid secretion. This knowledge leads to the therapeutic approaches/targets for ADPKD therapy. It has been shown that either reducing intracellular cAMP, inhibiting of cyst-lining epithelial cell proliferation pathways, or inhibiting transepithelial fluid secretion could retard renal cyst growth in both non-orthologous and orthologous animal models of ADPKD[5]. Interestingly, several natural compounds that are widely used as alternative medicine could reduce cystogenesis and improve renal function in animal model of ADPKD[6-9]. Due to the fact that cyst formation and progression involve several complex pathways, the effective treatment should inhibit or suppress several pathways in pathogenesis process of ADPKD. Therefore, target therapy of ADPKD requires the agents that can selectively target on several molecular

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pathways responsible for ADPKD development and causes fewer toxic effects on normal cells. This would be the most effective and ideal drug of choice. This review will focus on the pathophysiology and the therapeutic approaches for the treatment of ADPKD. Moreover, some of the natural compounds that are proposed to have high potential for the treatment of ADPKD will be discussed.

The pathophysiology of ADPKD

Pathophysiology of ADPKD is triggered by the loss of PC1 and/or PC2 functions. PC1 is composed of extracellular N-terminus, 11 trans-membrane protein, and intracellular C-terminus. It acts as a G-protein couple receptor (GPCR) which regulates signaling pathways involving in the development and differentiation of renal tubular cells. Whereas PC2 protein acts as a non-selective cation channel (TRP) to allow calcium influx into the renal tubular cell[10]. PC1 forms a functional complex with PC2 and acts as a mechanosensor to regulate intracellular calcium homeostasis. Thus, malfunction of these proteins causes a low level of intracellular Ca^{2+} which subsequently leads to increase cyclic AMP (cAMP) inside the cells[4,11]. The cAMP further stimulates cAMP-dependent cell proliferation and fluid secretion in ADPKD.

Several lines of evidence have shown that the progression of ADPKD involves proliferation of cyst-lining epithelial cell as well as fluid secretion in the cyst lumen[12-14]. Increasing cAMP levels could stimulate cell proliferation through cAMP-dependent B-Raf/MAPK/ERK pathway in PKD mouse model[14,15]. In addition, ERK 1/2 itself was also found to regulate mTOR activity via inhibition of tuberin protein (TSC1/TSC2)[16]. The mTOR signaling, another cell proliferation pathway, was upregulated in renal cyst-lining cells derived from ADPKD patient and mouse[16,17]. In addition, other signaling pathways such as, canonical Wnt/β-catenin signaling pathway[18-20], and cyclin-dependent kinase 2 (Cdk2), cell cycle activator[21,22] have also been reported to play an important role in cell proliferation in ADPKD pathogenesis.

One of a key factor of ADPKD pathogenesis is the hyperfunction of cystic fibrosis transmembrane conductance regulator (CFTR). It is a phosphorylation-dependent epithelial chloride channel activated by cAMP[13]. Chloride accumulation in cyst lumen causes luminal negativity that draws sodium and water movement in to the cyst. The basolateral side of renal epithelial cell has many transporters involving chloride transportation into the cell. Those include sodium potassium ATPase (Na^+-K^+ATPase), sodium potassium two chloride cotransporter 1 (NKCC1), and potassium channel KCa 3.1[23], whereas the apical membrane contains chloride channels such as CFTR[24] and calcium activated chloride channel (CaCC)[25]. Trans-epithelial chloride secretion involves chloride entry step via basolateral NKCC1 and exit step mostly via apical CFTR chloride channel which is activated by cAMP levels[26].

Therapeutic approaches in ADPKD

Most of ADPKD patients die with disease complications, especially end-stage renal disease[3]. Therefore, the goals for ADPKD intervention are reduction of morbidity, mortality, and increasing life span. At present, therapy of ADPKD patients are the supportive and symptomatic treatments including anti-hypertensive drugs, analgesic drugs for alleviating pain, antibiotics for preventing cyst infection, renal hemodialysis and kidney transplantation for maintaining body homeostasis[4,27]. Using both orthologous and non-orthologous animal models of ADPKD, it was shown that there are many promising candidate drugs which inhibit cyst progression and improve renal function[16,28]. Currently, several drugs have been approved in preclinical trials and entered human clinical trials[5,29]. At least, three promising approaches/targets including inhibition of cAMP such as vasopressin V2 receptor antagonists and somatostatin analogs, inhibition of cell proliferation such as mTOR inhibitors, and inhibition of fluid secretion such as CFTR inhibitors are in clinical studies and could represent the potential therapy of ADPKD.

Inhibition of cAMP

It is known that binding of aginine vasopressin peptide (AVP) to its V2 receptor at collecting duct stimulates adenylyl cyclases (AC) resulting in an increase in cAMP levels[30]. An increase in AVP level is thought to stimulate cyst growth and plays a role in cyst progression in PKD[31]. In preclinical trials, inhibition of AVP V2 receptor with OPC-31260, V2R antagonist, reduced cAMP level in renal tissues and inhibited cyst development in animal models of ADPKD ($Pkd2^{WS25/-}$)[32]. In addition to OPC-31260, OPC-41061 tolvaptan (an effective of V2 antagonist) potently reduced renal cyst progression in animal model of PKD and had specificity to human disease rather than other species[30].

Somatostatins, a peptide hormone-secreted

by pancreatic delta cells act on SST2 receptors (G_i-coupled receptor) which inhibits AC activity and cAMP production in both kidney and liver[33]. Octreotide, a long-acting somatostatin analogue, decreased cAMP levels resulting in suppression of cyst growth in kidney and liver of pck rats[34]. The results from pilot studies provided the opportunity for octreotide and lanreotide that are currently ongoing in preclinical and clinical trials for the treatment of polycystic kidney disease (PKD) and polycystic liver disease (PLD).

Inhibition of cell proliferation

mTOR is a serine-threonine kinase involved in the stimulation of cell proliferation and cell growth. Loss of PC1 function in ADPKD leads to increase in Rheb protein action, resulting in the activation of mTOR pathway and increased cell proliferation of cyst-lining epithelial cells. Rapamycin, a mTOR inhibitor, significantly slowed cyst growth in a non-orthologous animal model of PKD[35,36]. In addition, the derivatives of rapamycin have been shown to slow cyst growth in animal models of PKD. Currently, clinical trials of rapamycin and its analogs (everolimus) are in process.

Inhibition of fluid secretion

CFTR inhibitors (thaiazolidinone and hydrazide-containing compounds) have been shown to slow cyst enlargement in MDCK cyst growth model, embryonic kidney organ culture, and PKD mouse model[28,37]. In addition, a KCa3.1 inhibitor, TRAM-34, was also found to inhibit transepithelial chloride secretion in an acute phase of MDCK cell monolayers, in normal human kidney (NHK), and ADPKD cells. Interestingly, it also retards MDCK cyst growth and cyst formation. However, the efficacy of KCa3.1 inhibitors needs to be further determined in animal model of PKD[38].

Nutraceuticals for the treatment of ADPKD

Several natural products from herbs or plants are now widely used as ingredients in pharmaceutical agent and alternative medicine[39]. For ADPKD treatment, most of the current candidate drugs were synthetic compounds. Since some natural compounds seem to exert their effectson several pathways to inhibit PKD pathogenesis, thus, it is interesting to search for the natural compounds that have broad inhibition efficacy and high potency for the therapy of PKD pathogenesis. More importantly, those compounds should not produce any toxic or harmful to normal cells. Indeed, some natural plant-derived compounds such as triptolide, curcumin, ginkolide B, and steviol were found to have potency to slow renal cyst growth in cell and animal models of ADPKD and now some of them are in clinical trials.

Triptolide

Triptolide, a natural Chinese herb, is isolated from the medicinal vine, *Tripterygium wilfordii* Hook F, which is used in traditional Chinese medicine. It has anti-inflammatory and anti-cancer effects[40,41]. The recent studies reported that triptolide attenuated cyst growth in neonatal Pkd1 mice by inducing calcium release through a PC2-dependent pathway[42,43]. Moreover, the study using triptolide in adult transition Pkd1 mice found that triptolide slowed cyst growth and improved renal function[6]. At present, triptolide is investigated in clinical study.

Curcumin

Curcumin, a polyphenol diferuloylmethane, is extracted from *Curcuma longa* plant. It was found to have multiple effects including anti-inflammation, antioxidation, and anti-proliferation[44,45]. Recent study also reported that curcumin inhibited renal cystogenesis by suppressing cell proliferation pathways (ERK, p-S6, p-STAT3) in both MDCK cyst and Pkd1-deletion mouse[8,46].

Ginkolide B

Ginkolide B, a natural compound, derived from *Ginkgo biloba*, which is used as a traditional medicine in China. It was found to have anti-cancer and anti-inflammatory effect s[47]. Similarly, ginkolide B has been shown to inhibit cyst growth in MDCK cyst model and in *Pkd1* knockout mice through reduction of Ras/MAPK pathway[9].

Stevioside and its derivative (steviol)

Stevioside is a natural compound extracted from Stevia Rebuadiana plant. It is 300 times sweeter than sucrose. It is degraded by intestinal microflora to its aglycone, steviol, and is taken up into the blood circulation[48]. The biological activity studies of stevioside and steviol revealed that they have several therapeutic properties including anti-hypertensive[49], anti-hyperglycemic[50], anti-inflammatory[51], and anti-diarrheal effect[52], and they also enhance muscle recovery from injury[53]. In addition, they exert inhibitory effect on renal organic anion transporter[54,55] which could delay an excretion of therapeutic drug resulting in enhancing its efficacy. Our recent studies revealed

that steviol and its derivatives reduced MDCK cyst formation and growth through the direct inhibition of CFTR activity and promotion of protreasome-mediated CFTR degradation[56]. More important, stevioside and steviol also retarded cystogenesis and improved renal function in Pkd1$^{-/-}$ mice by activation of AMP-activated protein kinase which inhibited CFTR and mTOR/S6K protein expression[7]. Because steviol can effectively inhibit several pathways in pathogenesis of ADPKD with no toxic effect at low dose, it seems to be a novel compound for ADPKD therapy. However, further study in modifying the structure of steviol is needed to minimize its effective dose.

Conclusion

Autosomal dominant polycystic kidney disease is a common genetic renal progressive disease, which could lead to end-stage renal failure, and there is no effective intervention presently. Several drugs are under clinical studies including vasopressin antagonists, somatostatin analogs, and mTOR inhibitors. Interestingly, many natural compound such as triptolide, curcumin, ginkgolide B, and steviol that were shown to have potency to slow cyst growth and some can improve renal function are in preclinical and clinical trials. Taken together, it is convincing that the combination therapy between drug and natural compound might be an alternative way to increase the therapeutic efficacy of ADPKD. However, this approach needs further clinical investigation for the benefit versus the side effect.

What is already known on this topic?

The previous studies reported the general concept of pathology and the treatment of autosomal dominant polycystic kidney disease. Some studies showed the effect of natural compounds for inhibiting cyst progression in polycystic kidney disease.

What this study adds?

This review focuses on the pathophysiology, the therapeutic approaches, and the natural compounds used in autosomal dominant polycystic kidney disease. In addition, the potent nutraceuticals and the detailed mechanisms for ADPKD therapy were summarized and indicated here.

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Potential conflicts of interest

None.

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สารสกัดจากพืชสมุนไพรเพื่อใช้รักษาโรคถุงน้ำในไต

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โรคถุงน้ำในไตเป็นโรคทางพันธุกรรมของไตที่พบบ่อยที่สุด เกิดจากการผ่าเหล่าของจีน PKD1 และ/หรือ PKD2 ถุงซีสต์ถูกสร้างขึ้นจากกระบวนการแบ่งตัวแบบผิดปกติของเซลล์ท่อไตจนกลายเป็นซีสต์ (cell proliferation) ร่วมกับการหลั่งคลอไรด์ (fluid secretion) ลงสู่ถุงซีสต์ทำให้ซีสต์ขยายขนาดขึ้นและกดเบียดทำลายเนื้อไตนำไปสู่การเกิดโรคไตวายเรื้อรัง ปัจจุบันยังไม่มีการรักษาใดที่มีประสิทธิภาพ อย่างไรก็ตามความสัมพันธ์ระหว่างฤทธิ์การรักษาโรคของสารสกัดจากพืชสมุนไพรและกระบวนการเกิดพยาธิสภาพของโรคถุงน้ำในไต ทำให้นักวิจัยเกิดความสนใจศึกษาฤทธิ์ของสารสมุนไพรเพื่อใช้รักษาโรคถุงน้ำในไตอย่างแพร่หลาย ปัจจุบันมีสารสกัดจากพืชสมุนไพรหลายชนิดอาทิ triptolide, curcumin, ginkolide B, และ steviol ที่สามารถชะลอการเติบโตของซีสต์ในหนูโมเดลโรคถุงน้ำในไตได้ โดยสารเหล่านี้มีกลไกยับยั้งการเติบโตของซีสต์คือ สาร triptolide เพิ่มการหลั่งแคลเซียมภายในเซลล์ท่อไต, สาร curcumin ยับยั้งการทำงานของกลไก ERK และ p-STAT 3, สาร ginkolide B ยับยั้งการทำงานของกลไก Ras/MAKP, และสาร steviol กระตุ้นการทำงานของโปรตีน AMPK ส่งผลให้ยับยั้งการทำงานของโปรตีนขนส่งคลอไรด์ CFTR อีกทั้งยังยับยั้งการทำงานของกลไก mTOR ทั้งในเซลล์และหนูโมเดลโรคถุงน้ำ นอกจากนี้สารสมุนไพรเหล่านี้อยู่ในขั้นตอนของการพัฒนาในสัตว์ทดลองและมนุษย์ให้เป็นยารักษาโรคถุงน้ำในไตตามลำดับ การทบทวนวรรณกรรมนี้เน้นบรรยายเกี่ยวกับพยาธิสรีรวิทยาของโรคถุงน้ำในไตและการรักษาในปัจจุบัน โดยเฉพาะการนำเอาสารสกัดจากพืชสมุนไพรเพื่อพัฒนาเป็นยาที่มีประสิทธิภาพในการรักษาโรคถุงน้ำในไต