REVIEW ARTICLE

Medicinal Plants Used in Thailand for Treatment of Kidney Failure

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Abstract

Kidney failure is one of the most serious health problems in Thailand with high health care cost, mortality, and prevalence rate. Traditional herbal medicines constitute a promising source of active chemical constituents that can be exploited as novel therapeutic agents for kidney dysfunction. This review focuses on the biological and pharmacological activities including the potential roles of the medicinal plants used in Thailand for treatment of kidney failure. The review summarizes some fundamental aspects of medicinal plants used in Thailand which have been reported to improve kidney function. In addition, the major medicinal plants are discussed on phytoconstituents and pharmacological activities of the herbs.

Keywords: Medicinal plants, alternative medicine, kidney failure, Thailand

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พืชสมุนไพรรักษาไตวายในประเทศไทย

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บทคัดย่อ

โรคไตวายนับว่าเป็นปัญหาสาธารณสุขที่รุนแรงที่สุดโรคหนึ่งในประเทศไทย โดยมีค่าใช้จ่ายในการรักษา อัตราการเสียชีวิต และอุบัติการณ์การเกิดโรคสูงมาก สมุนไพรพื้นบ้านเป็นแหล่งที่อุดมไปด้วยองค์ประกอบทางเคมีที่มีฤทธิ์ทางชีวภาพโดยสามารถนำไปพัฒนาเป็นยารักษาโรคไตวายได้ในอนาคต บทความปริทัศน์นี้เป็นบทความที่มุ่งเน้นฤทธิ์ทางเภสัชวิทยาที่สำคัญของพืชสมุนไพรที่ใช้รักษาโรคไตวายในประเทศไทย โดยสรุปข้อมูลรายงานการวิจัยของพืชหลายชนิดที่พบว่ามีฤทธิ์ทางเภสัชวิทยาที่สามารถกระตุ้นการทำงานของไตให้ทำงานอย่างปกติ อีกทั้งยังสรุปองค์ประกอบทางเคมีและฤทธิ์ทางเภสัชวิทยาอื่นๆ ที่สำคัญที่พบได้ในพืชสมุนไพร

คำสำคัญ: พืชสมุนไพร, การแพทย์ทางเลือก, โรคไตวาย, ประเทศไทย

Introduction

Kidney failure is one of the most serious health problems in Thailand with high health care cost, mortality, and prevalence rate. Based on the statistics of the Ministry of Public Health of Thailand, kidney failure has gradually increased during the past two decades.[1,2] It is more common in Thai females than Thai males. Major health risks include hypertension and diabetes.[1] Uncontrolled high blood pressure can damage blood vessels and nephrons in the kidneys, whereas long-standing diabetes can alter the integrity of small blood vessels leading to kidney damage.

Kidney failure can be divided into two categories, acute kidney injury and chronic kidney disease. Acute kidney injury (AKI)[3] or acute renal failure is defined as a condition in which the loss of kidney function is rapid and progressive, but is potentially reversible. This condition is caused by a number of factors including hypovolemia, oedematous states, sepsis, ischemia, rhabdomyolysis, drug-induced toxicity, pre-existing kidney disease, or obstructive injury. The decline in glomerular filtration rate (GFR), retention of nitrogenous waste, fluid and acid, and disturbance in electrolyte balance is rapid. Most can be treated and the kidney function gradually returns to normal condition. Current therapy aims mainly at prevention and treatment of the associated complications. In severe AKI, replacement of the kidney function by dialysis (artificial kidney), or transplantation is necessary. Chronic kidney disease (CKD)[4] or chronic renal failure is defined as a slow and gradual loss of kidney function characterized by a decrease in glomerular filtration rate (GFR) and histologic evidence of a reduction in nephron population. CKD is usually an irreversible and progressive disease, ultimately leading to end-stage renal disease (ESRD). The primary cause of CKD is diabetes and hypertension, but can also be due to glomerulonephritis, interstitial nephritis, hereditary kidney disease (polycystic kidney disease), and autoimmune disorders (systemic lupus erythematosus). Patients with early stage CKD can be treated with medication and adjustment of lifestyle to prevent or delay disease progression and onset of kidney failure. When the impairment of kidneys progresses to advanced stage, the only treatment option is renal replacement therapy by hemodialysis or kidney transplantation. The prevalence rate of patients receiving renal replacement therapy (RRT) in Thailand was reported to be tripled from 2007 to 2015.[2] The incidence of hemodialysis, peritoneal dialysis, and kidney transplantation were respectively, increased from 62.83, 55.60, and 4.85 *per* million populations in 2009 to 168.01, 140.56 and 9.14 *per* million populations in 2015. Despite substantial advances in supportive care, the number of new cases of CKD and patients on dialysis continues to be increased, and morbidity and mortality rates remain high. Due to high cost of dialysis, treatment or medication is not affordable for a number of patients, and this has led to an increase in the mortality rate during the past years. Preventing the progression and complication arising from kidney failure has therefore become an issue of concern.

Traditional herbal medicines constitute a promising source of active chemical constituents that can be exploited as novel therapeutic agents for kidney dysfunction. Thailand has a long history of using medicinal plants for a variety of diseases or health conditions, either as dietary supplements or alternative medicines. Several medicinal plants have been claimed to promote proper kidney functions or increase urinary output due to their diuretic activity.[5-8] This review focuses on the potential

roles of medicinal plants used in Thailand for treatment of kidney dysfunction. Table 1 summarizes information on medicinal plants including their parts used.

Table 1. Major medicinal plants used in Thailand for treatment of kidney dysfunction.

Family	Plant	Part used	Effect on renal function
Ganodermataceae	*Ganoderma lucidum*	Fruit body, spores, mycelia	Nephroprotective, hypotensive, ACE inhibiting activity
Moraceae	*Morus alba*	Leaves, fruit, bark root	Nephroprotective
Poaceae	*Zea mays*	Corn silk	Nephroprotective, diuretic activity
Euphorbiaceae	*Phyllanthus amarus*	Leaves	Hypotensive, nephroprotective, diuretic activity
Zingiberaceae	*Boesenbergia rotunda* (L.) Mansf.A.	Rhizome	Nephroprotective, diuretic activity
Poaceae	*Imperata cylindrica* (L.) Beauv.	Rhizome, leaves	Nephroprotective, diuretic activity, hypotensive

NOTE: The references are provided in the text; ACE = angiotensin-converting enzyme

Ganoderma lucidum (Curtis) P. Karst

Ganoderma lucidum in the family Ganodermataceae, is an oriental fungus known as Reishi, Ling Zhi, or Mannentake. Its fruit body is a large, dark red mushroom with a glossy exterior and a woody texture. It naturally grows on fallen trees and rotting wood.[9] *G. lucidum* has a long history of traditional use in China and other Asian countries for promoting health and longevity as health supplement and herbal medicine. Different parts of *G. lucidum*, including fruit body, spores, and mycelia, contains various pharmaceutically active compounds which are used for numerous indications including for the control of blood glucose levels, modulation of the immune system, hepatoprotection, and bacteriostasis.[9]

Major bioactive constituents and pharmacological activities *G. lucidum* contains polysaccharides, triterpenes/triterpenoides, nucleotides, sterols, steroids, fatty acids, proteins/peptides, and trace elements.[10] The biologically active *G. lucidum* polysaccharides are mainly in the form of β-*D*-glucans, the polysaccharides of *D*-glucose monomers linked together by β-glycosidic linkages.[11] The basic chemical structures of the triterpenes from *G. lucidum* are lanosterol, an important intermediate in phytosterol biosynthesis pathway, as well as other triterpenes such as ganoderiols, ganoderic acids, and lucidenic acids.[10,12] Several polysaccharides and triterpenes compositions of *G. lucidum* exhibit antiproliferative[13,14], anti-oxidant[14], immuno-modulating[15], hypoglycemic[16], and antiplatelet aggregation[17] activities.

The potential role in kidney diseases The potential role of *G. lucidum* for the control of kidney function is principally based on its anti-oxidation, antiplatelet aggregation, and immunomodulating activities, that prevent development and progression of kidney failure. The anti-oxidant activity of *G. lucidum* was demonstrated to protect the kidneys from progression to dysfunction stage in various *in vitro* and *in vivo* studies.[18,19] Ganodermic acid S from *G. lucidum* exhibited a mild to moderate inhibitory effect on platelet aggregation.[20] Active constituents with antiplatelet aggregation activity may exert their activity through improving blood flow, and preventing renal vein thrombosis. However, this activity may also increase the risk of hemorrhage. The immunomodulating effect of the polysaccharide constituents may play a potential role in the treatment of CKD patients associated with autoimmune diseases.[21] *G. lucidum* extract was also shown to produce significant hypotensive effect and reduce the risk of CKD. Triterpenoid from *G. lucidum* extract exhibited inhibitory activity on angiotensin-converting enzyme (ACE) activity *in vitro*.[22] In a double-blind clinical study, *G. lucidum* extract at the dose of 55 mg given three times a day, significantly reduced high blood pressure (systolic and diastolic) in hypertensive patients who were not responded to antihypertensive medicines.[23] The crude extract of *G. lucidum* was reported to be a promising treatment of Thai patients with nephrosis and focal segmental glomerulo-sclerosis.[5,24] The extract at the dose of 750 to 1,100 mg/day given together with vasodilators (enalapril, isradipine, and dipyridamole) improved immunological balance and eliminated proteinuria in this group of patients who were not responded to immunosuppressive drugs (cyclophosphamide, and/or corticosteroids).

Morus alba Linn.

Morus alba or white mulberry belonging to Moraceae family, is a moderately sized shrub or tree with white, greenish white, purple or blackish purple aggregate fruit (syncarp). White mulberry has a long history of medicinal use in Chinese medicine for various indications, *i.e.*, treatment of fever, sore throat, dyspepsia, anemia, urinary incontinence, tinnitus, dizziness, cardiovascular disorder, and diabetes.[25]

Major bioactive constituents and pharmacological activities *M. alba* contains the bioactive components including alkaloids, anthocyanins, and flavonoids. A piperidine alkaloid (1-deoxynojirimycin: DNJ) was identified as a major constituent of *M. alba* leaf, root bark, and fruit.[26] Mulberry leaf is one of the richest sources of various flavonoids[27], while the fruit contains abundance of anthocyanins.[26] Bioactive constituents from *M. alba* leaf and root bark have been reported to possess antimicrobial[28], anti-oxidant[29], antiproliferative[29], hypoglycemic[30], and immune system-stimulating[31] properties.

The potential role in kidney diseases The hypotensive and diuretic effects of *M. alba* root bark were reported in mice, rats, guinea pigs, and dog.[32] The extract produced significant nephroprotective effect which resulted in preventing the development and progression of kidney failure. Nematbakhsh *et al.*[6] demonstrated that the flavonoid fraction from *M. alba* leaves significantly inhibited cisplatin-induced nephrotoxicity and increased blood urea nitrogen and creatinine in rats. The promising role of *M. alba* for treatment of hyperuricemic patients with renal

dysfunction has been demonstrated.[33] Mulberroside A, the stilbene glycoside of *M. alba,* produced uricosuric and nephroprotective effects in oxonate-induced hyperuricemic mice. It decreased serum levels of urea nitrogen, creatinine, albumin, and β-microglobulin, and urinary *N*-acetyl-β-*D*-glucosaminidase activity.[33] In addition, the water extract of *M. alba* markedly attenuated hypertension, hyperlipidemia, and vascular dysfunction in rats fed an atherogenic diet.[34]

Corn silk of *Zea mays* Linn.

Maize (*Zea mays* L.) or corn, belonging to Poaceae (Gramineae) family, is a commonly cultivated cereal crop grown widely throughout the world. It is used as human food and livestock feed. Corn silk or *Stigma maydis* (stigmata of maize female flowers of *Z. mays*) is the fine soft, yellowish thread-like strands found inside the husks of corn. Corn silk is a well-known traditional Chinese herbal medicine used to control obesity, edema, cystitis, gout, kidney stone, prostate disorder, and urinary infections.[35,36]

Major bioactive constituents and pharmacological activities Corn silk has been reported to contain various compounds with diverse chemical structures, *i.e.*, proteins, vitamins, mineral salts, alkaloids, volatile compounds, flavonoids, saponins, tannins, phenols, steroids, carbohydrate, and polysaccharides.[35-37] Multiple biological and pharmacological activities of corn silk have been demonstrated in various experimental models. It exhibits anti-oxidants[35], antimicrobial[38], anti-inflammatory[39], anticoagulant[40], antipigmentation[41], antiproliferative[42], and anti-obesity[43] activities.

The potential role in kidney diseases Corn silk extract has been reported to exhibit diuretic and kaliuretic activities in water-loaded conscious rats.[36] The diuretic effect of the aqueous extract was demonstrated at the dose of 500 mg/kg body weight, while the kaliuretic (potassium urinary excretion) activity was shown at the dose of 350 and 500 mg/kg body weight. The glomerular filtration and filtered load were decreased without affecting proximal tubular function, sodium ion, or uric acid excretion. The diuretic effect of corn silk has been well demonstrated in various studies. Its diuretic activity through increasing excretion of sodium and potassium was well demonstrated in anesthetized Wistar rats.[44] This diuretic activity is exploited for treatment of edema as well as cystitis, kidney stones, and nephritis.[45-47] The nephroprotective effect of the plant extract is mainly due to its anti-oxidative activity. Sepehri *et al*. demonstrated that the methanolic extract of corn silk prevented gentamicin-induced interstitial nephritis in rats.[7] In rats with kidney failure, corn silk extract in combination with binahong leaves significantly improved animal's renal function.[48]

Phyllanthus amarus Schum. & Thonn.

Phyllanthus amarus or "Bhuiamlaki" belonging to Euphorbiaceae family, is a small annual herb that grows 30-40 cm in height. It is the most widespread species of the *Phyllanthus* genus and distributed in all tropical regions of the world. *Phyllanthus* has a long history of its traditional use in Indian Ayurvedic medicine. The leaf of *P. amarus* is widely used for treatment of diabetes, intestinal infection, and liver, kidney and bladder dysfunctions.[49]

Major bioactive constituents and pharmacological activities The major bioactive constituents of *P. amarus* are lignin, flavonoids, hydrolysable tannins, alkaloids, triterpenes, and volatile oil.[49-51] *P. amarus* is a rich source of phytochemicals that can produce a number of pharmacological effects, including antimicrobial, anti-inflammatory, anti-oxidant, antiviral, antitumour, hepatoprotective, gastroprotective, and anti-ulcer activities.[49,52]

The potential role in kidney diseases The diuretic, hypotensive, and hypoglycemic effects of *P. amarus* on human subjects were reported by Srividya and Periwal.[8] Significant increase in 24-h urine volume, and urinary and serum sodium levels was demonstrated in hypertensive patients following treatment with *P.amarus* for 10 days. In addition, significant reduction in systolic blood pressure was observed in patients with non-diabetic hypertension. Amaechina and Omogbai[53] reported that the aqueous extract of the leaves of *P. amarus* produced significant reduction in the mean diastolic, systolic and arterial pressures in a dose-dependent manner.

Boesenbergia rotunda (Linn.) Mansf.

Boesenbergia rotunda (fingerroot) belonging to Zingiberaceae family, is ginger species known as Chinese ginger or "TemuKunci" in Indonesia and Malaysia or as "Krachai" in Thailand. This plant has eight synonym names, *i.e., Boesenber giacochinchinensis* (Gagnep.) Loes., *Boesenbergia pandurata* (Roxb.) Schltr., *Curcumarotunda* L., *Gastrochilus panduratus* (Roxb.) Ridl.,*Gastrochilus rotundus* (L.) Alston, *Kaempferia cochinchinensis* Gagnep., *Kaempferia ovata* Roscoe, and *Kaempferia pandurata* Roxb. *B. rotunda* is a small perennial plant with bright yellow, short (2 cm) and globular shaped rhizomes which has several slender and long tubers sprouting from the central part all in the same direction like the fingers of a hand.[54] Its rhizome is commonly used in Southeast Asia as a food ingredient and folk medicine for treatment of aphthous ulcer, dry mouth, stomach discomfort, peptic ulcer, leucorrhea, dysentery, and diuresis.[55-57]

Major bioactive constituents and pharmacological activities The rhizomes, leaves and stems of *B. rotunda* contain several bioactive compounds such as flavonoid derivatives, chalcone derivatives, esters, essential oils, kawains, terpenes, and terpenoids.[58] The rhizome of *B. rotunda* contains bioactive constituents with antimicrobial activity against various bacteria, fungi, yeast, and parasites.[57,59] *B. rotunda* rhizome was also shown to possess anti-inflammatory[60], anti-oxidant[59,60], antiproliferative[60], anti-ulcer[55], and anti-amoebic[56] activities.

The potential role in kidney diseases The traditional use of *B. rotunda* rhizome extract has been reported for diuresis.[58] With the application of least square analysis (OPLS) to calculate the correlation between metabolite profiles and adenosine A1 receptor binding activity, the two possible active compounds flavonoid derivatives, pinocembrine and hydroxy-panduratin from *B. rotunda* rhizome extract, were shown to bind to adenosine A1 receptor.[61] Flavonoid is one of natural antagonist ligands for adenosine A1 receptor and the antagonistic activity to this receptor is known to be associated with diuretic activity. The essential oil from *B. rotunda* rhizome (1.2%) was shown to solubilize calcium kidney stone.[62] Furthermore, the potent anti-oxidant activity of the *B. rotunda* rhizome extract was also shown to link to the protection of kidney against oxidative stress.

Imperata cylindrica (L.) Beauv.

Imperata cylindrical belonging to Poaceae family, is a warm-season, perennial, rhizomatous grass species known as cogongrass, Japgrass, blady grass, spear-grass, alang-alang, and orlalang-alang. Cogongrass is the most troublesome weeds worldwide which is found throughout the tropical and subtropical regions of the world.[63] Young leaves appear light green, while older leaves become orange-brown to dark brown in colour. The dead leaves remain standing and resist decay.[64] The plant is used for soil stabilization, roofing thatch, paper industry, and weaving. With regard to its traditional use, *I. cylindrical* extract is a reputed drug mentioned in the ancient books of Indian Ayurvedic medicine for treatment of urinary calculi, retention of urine, diabetes, cardiac disorders, gout, common cough and cold, and anemia.[65]

Major bioactive constituents and pharmacological activities The major phytochemical constituents from *I. cylindrica* are tannins, saponins, flavonoids, terpenoids, cardiac glycosides, alkaloids, triterpenoids, lactones, sterols, organic acids, coumarins, flavones, chromones, and other phenolic compounds.[66,67] Different constituents from various parts of *I. cylindrica* were demonstrated to possess biological and pharmacological activities including antimicrobial[68], antiproliferative[69], analgesic[70], anti-inflammatory[70], and inhibitory activities on germination and seedling growth.[64]

The potential role in kidney diseases The *I. cylindrica* rhizome extract is used in traditional medicine for diuresis. However, experimental studies did not provide evidence to support this traditional use. The aqueous extract of *I. cylindrica* rhizome at doses equivalent to 5 and 10 mg/kg body weight apparently inhibited the urination of adult Sprague-Dawley rats.[71] In a randomized, placebo designed cross-over trial in 40 healthy volunteers (2 cohorts of 20 subjects), *I. cylindrical* rhizome extract produced no effect on 12- and 24-h urine output or sodium excretion.[47] The hypotensive effect of *I. cylindrica* rhizome extract has been reported in animal studies. The rhizome of *I. cylindrica* was found to contain two lignans namely graminones A and B. The inhibitory action of graminone B on the aorta was demonstrated in rabbit.[72] The antihypertensive property of the leaf extract of *I. cylindrica* was also demonstrated in cat, and the vasodilative effect on jejunum smooth muscle was demonstrated in rabbit.[73]

Conclusion

Numerous medicinal plants are used in alternative medicine for treatment of kidney failure in Thailand. Some of them have been well explored, while others have been used entirely based on traditional use, empirical support or extrapolation from animal studies without supporting evidence from clinical studies. Future research should focused on a battery of *in vitro,* animal and human studies to confirm their traditional uses. In addition, identification of their active constitutes that are responsible for their renal protective activities as well as investigation of their molecular and cellular mechanisms of action are required.

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