Chin J Integr Med 2012 Oct;18(10):

REVIEW

Phytochemical Analysis of Medicinal Plants with Kidney Protective Activities

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ABSTRACT In view of the increasing number of patients undergoing kidney dialysis or transplant every year, a survey of the literature on renal protective medicinal plants was undertaken. Most of them are from traditional Chinese medicine (TCM). Although many of the medicinal herbs reported have not been investigated in terms of active chemical ingredients, some do have compounds well characterized. They fall into a wide range of structures. Several groups of compounds with well established activities are discussed. These include: antioxidant phenolic compounds like tannins, flavonoids, isoflavonoids, unsaturated organic acids and lignans; circulation enhancing compounds like saponins, and basic alkaloids with multiple targets (G-protein coupled receptors). Also presented are proinflammatory and antiinflammatory fatty acids like linoleic (n-6) and α-linolenic (n-3) acids, respectively. Attention is also drawn to the plants containing nephrotoxic aristolochic acid. Different directions of future research are also presented. We hope that this review may provide some leads for new drug discovery and development, and more rational application of TCM.

KEYWORDS kidney protective herbs, kidney protection natural products, antioxidants, free radical scavengers, immunomodulating agents, antiinflammatory agents, structure-activity relationship, physicochemical parameters

From our literature survey[1-7], there are 174 species of plants belonging to 78 families, plus 2 minerals and 3 animals reported to have kidney protective activities. This is intriguing considering the fact that many commonly prescribed drugs are known to be associated with nephrotoxicities, like analgesic and non-steroidal antiinflammatory drugs, sulfonamides, aminoglycosides and cephalosporins[8-11], but relatively few are known to have nepheroprotective effects, e.g., diuretics mannitol and furosemide in preventing cisplatin nephrotoxicity[10].

The purpose of this review is to examine the long standing traditional Chinese medicine (TCM) in the area of medicinal plants used in the treatment of kidney disease and/or kidney protection, and to sort out the most common chemical ingredients and their possible mechanisms of action. This is important in view of the increasing number of patients undergoing kidney dialysis or transplantation every day. In this arena, prevention certainly is better than highly invasive treatments with high cost and some times less than desirable outcome.

Botanical Analysis

Among these families of plants listed in Table 1, compositae has 12 species and leguminosae has 11 species reported to have kidney protective activities. Some of the plants and ingredients listed have been associated with nephrotoxicity. For example, aristolochic acid has been reported to cause nephropathy, Fanconi syndrome and progressive renal failure[12-14]. Until proven otherwise, it is wise to stop using those plants known to contain aristolochic acid (e.g., *Aristolochia manshuriensis, Akebia quinata, Clematis armandi* and *Clematis montana*). Of the 174 species, 34 have previously been reported to have liver protective activities[15]. This is in agreement with the classification of the channels entered by the specific plants according to the theory and practice of TCM, namely that many of these plants (e.g., *Rehmanaia glutinosa, Cinnamomum cassica, Cornus officinalis* and *Plantago asiatica*) are known to enter the Shen (肾) and the Gan (肝) channels[7]. A most commonly used Chinese herb licorice (*Glycyrrhiza*

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DOI: 10.1007/s11655-011-0713-3

uralensis) is known to enter 12 channels[7], in addition to its ability to cover up unpleasant taste of many plants due to its sweet ingredient glycyrrhizine (50-fold the taste of sucrose on the weight basis).

Biochemical and Phytochemical Analysis

Several different mechanisms have been proposed for anagelsic associated nepheropathy: (1) direct toxic effect by the high concentration in the medullary tissue (loop of Henle); (2) anoxia caused by vasoconstriction or mesangial thickening, platelet aggregation, occlusion of blood vessels by interstitial hyperplasia, changes in the oxygen binding of hemoglobin, and changes in blood viscosity; (3) metabolic effects, e.g., reduced intracellular adenosine triphosphate (ATP) and glucogenesis, and uncoupling of oxidative phosphorylation by salicylates and some phenolic compounds; (4) inhibition of prostaglandin biosynthesis[8].

Antioxidant polyphenols may prevent nephropathy by interfering with the generation of reactive oxygen species or free radicals. Bioactivation and subsequent covalent bond formation have been implicated in both hepatotoxicity and nephrotoxicity[8-11]. Many of the antioxidants found in TCM are known to contain ingredients with oxidizable functional groups, e.g., unsaturated organic acids such as ferulic acid and isoferulic acid, flavonoids, isoflavonoids, and tannins[15]. The number of renal protective plants (174 species) is less than that of hepatoprotective plants (274 species)[15], which may be due to the first pass metabolism where many compounds are metabolized, some to inactive metabolites in the gastrointestinal tract and the liver.

Phytochemicals like saponins may improve microcirculation due to their surfactant properties. Examples of plants containing saponins include *Zea mays (*style and stigma)*, Glycyrrhiza uralensis, Bidens bipinnata* and *Forsythia suspensa*.

Biologically active alkaloids may have multiple mechanisms of action due to their basic nitrogen functional group, which may interact with G-protein coupled receptors[16]. Due to the acidic pH in the urine, they may also be more concentrated in the kidney than in the blood. Further studies are needed to identify the exact mechanisms of each specific alkaloid.

Among the plants listed in Table 1, 20 have been reported to have diuretic activities. It remains to be examined whether they exert diuresis by increasing renal blood circulation or by inhibition of renal tubular reabsorption of the filtrate.

In TCM, Shen is associated with sexual function, so are the drugs affecting renal function. Many of the renal protective plants contain flavonoids and/or isoflavonoids. We have reported that many isoflavonoids and lignans have estrogenic activities while flavonoids have antiestrogenic activities[17,18]. In the practice of TCM, combinations of herbs are used to treat various diseases. The formula used is based on the diease state of the patient, and the key is to maintain a proper balance between yin and yang. In modern terminology, it may mean a balance between the intake of estrogenic and anti-estrogenic compounds; and a balance between the intake of pro-inflammatory and antiinflammatory substances[19].

Several of the plants in Table 1 contain essential fatty acids like linoleic acid and linolenic acid (*Lobaria pulmonavia, Bupleurum chinensis*). The antiinflammatory property of α-linolenic (n-3) faty acid and the proinflammatory effect of linoleic acid (n-6) acid have been reported[19,20]. A balance between extracellular and intracellular signaling[21] will undoubtedly become an important area of investigation. Table 2 shows the diverse structures of the chemicals with renal protective or toxic activities. The interaction among the immune response, proinflammatory, antiinflammatory and renal protective agents are shown in Figure 1.

Structure-Activity Relationship Analysis

Among the representative structures presented in Table 2, the molecular weights range from 165 (ephedrine) to 869 (dioscin), and ClogP values range from 0.59 (dioscin) to 6.82 (linolenic acid). The E_{lumo} values extend from −1.32 (justicidin C) to 1.25 (diosgenin). E_{lumo} is a measure of the reactivity as an electrophile, whereas ClogP is a measure of lipophilicity. A glycoside like dioscin is comprised of a lipophilic aglycone (diosgenin) and three hydrophilic sugar moieties, resulting in an amphiphilic (surfactant like) compound with ClogP of only 0.59 while that of the aglycone is 5.91. These parameters and the range of dipole moment (1.86−7.96D) suggest not only multiple sites of action, but also different mechanisms

Table 1. Medicinal Plants Reported to Have Kidney Protection Properties[1-4]

Family name	Latin name	Ingredient	(Liver protection) (+) [Comments]
Acanthaceae	*Rostellularia procumbens*	Justicidin C, D	(+)
Alismataceae	*Alismatis plantago-aquatica subsp orientale*	Triterpenoids: alisol A, B, C; sugars, amino acids, lecithin, choline, vitamins, protein, potassium, β-sitosterol	[Diuretic]
Amaranthaceae	*Achyranthes aspera*	Achyranthine, ecdysterone	
Annonaceae	*Desmos chinensis*		
Apocynaceae	*Apocynum venetum*		
	Parameria laevigata		
	Wrightia pubescens		(+)
Aquifoliaceae	*Ilex chinensi*		
	Ilex rotunda	Flavonoid glycoside, phenols, tannins, β-sitosterol, ilex, triterpenoid saponin, β-amyrin, oleanolic acid, rotundic acid, ilexin A & B, amino acid, carbohydrate, saponin	(+)
Araliaceae	*Aralia armata*		(+)
	Aralia chinensis	Triterpene glycosides, tannins, choline, volatile oil	(+)
Aristolochiaceae	*Aristolochia manshuriensis*	Aristolochic acid, akebin (a saponin), hederagenin, oleanolic acid, akebosides stb, stc, std, ste, stf, sth, stj, stk	[Diuretic] [Nephrotoxic][12-14]
Asclepiadaceae	*Cynanchum auriculatum*		
	Cynanchum atratum	Cynanchol, volatile oil	
	Metaplex japonica	Benzoylramanone, metaplexigenin, isoramanone,sarcostin, gagaminin, dibenzoylgagamiol, deacylcynanchogenin, pegularin, utendin, D-cymarose, digitoxose kidjolanin, lineolon, 7 α-hydroxy-12-O-benzyl-deacylmetaplexigenin	
	Streptocaulon griffithii		
Berberidaceae	*Berberies vulgaris*	Berbamine oxyacanthine	[Bisbenzylisoquinoline, alkaloid]
Betulaceae	*Betulla platyphylla var Japonica*	Sinapic acid, apigenin, betulafolienetriol, 3-epiocotillol, hydroxyl hopanone	
Bignoniaceae	*Catalpa ovata*	Ferulic acid, isoferulic acid, p-coumaric acid, menaquinone-1, 8-hydroxydehydro-iso- α-lapachone, α-lapachone, 4-hydroxy- α-lapachone, 9-hydroxy- α-lapachone, 4,9-di- hydroxy- α-lapachone, 1-hydroxy-2-methylanthraquinone, catalpalactone, catalpinoside, 9-methoxy- α-lapachone	
Boraginaceae	*Cynoglossium lanceolatum*		
Campanulaceae	*Lobelia chinensis*	Lobeline, lobelanine, lobelanidine, isolobelamine	[Diuretic]
Caprifoliaceae	*Sambucus adnata*		
	Sambucus javanica		
	Sambucus williamsii		
Caryophyllaceae	*Cucubalus baccifer*		
	Stellaria yunnanensis		
	Dianthus superbus	Saponin, essential oil-eugenol	[Diuretic]
Celastraceae	*Celastrus stylosus*		
Clavicipitaceae	*Cordyceps sinensis* (grows on the larva of caterpillar)	Polysaccharides	
Commelinaceae	*Cyanotis vaga*	Commisterone	

(To be continued)

Family name	Latin name	Ingredient	(Liver protection) (+) [Comments]
Compositae	*Anisliaea spicata*		
	Artemisia lactiflora		
	Atractylodes ovata	Atractylon, atractylol, vitamin A	[Diuretic]
	Atractylodes japonica	Atractylon, sesquiterpene, furfural	[Diuretic]
	Bidens bipinnata	Saponins, flavonoids, alkaloids	
	Carpesium abrotanoides	n-caproic acid, oleic acid, pinoleic acid; granilin, carabrone, carpesialactone	
	Elephantopus scaber	Deoxyelephantopin, isodeoxyolephantopin, lupeol acetate	
	Emilia sonchifolia	Alkaloids, phenols	
	Leontopodium leontopodioides		
	Senecio integrifolius		
	Senecio nagensium		
	Xanthium sibiricum		
Convovulaceae	*Pharbitis nil*	Ipurolic acid, pelargonin, paeonidin, paeonin, 2-O-β-glucosyl-gibberellenic acid, pharbitic acid, pharbitin, nilic acid, gallic acid, 2-O-β-glucosyl-gibberellin-A_3, A_8, A_{27}, A_{29}	
Cornaceae	*Cornus officinalis*	Glycosides: morroniside, sworoside, loganin, longiceroside, 7-O-methylmorroniside, morroniside, sweroside; triterpenoids: ursolic acid; saponin: cornin; organic acid: tartaric acid, malic acid, gallic acid	[Diuretic]
Cruciferae	*Thlaspi arvense*	Sinigrin→(C_3H_5N=C=S)	
Curcurbitaceae	*Actinostemma lobatum*		
	Benincasa hipida		
	Citrullus vulgaris	Cis, cis-3,6-nonadien-1-ol, L-β(pyrazol-1-yl)alanine, (β-imidazolyl-N)-alanine	
Dioscoreaceae	*Dioscorea sativa*	Dioscin →(diosgenin + rhamnose + glucose)	
	Dioscorea tokoro	Dioscin, gracillin, trillin, dioscorea sapotoxins A, B; diosgenin, tokorogenin, kokagenin, yonogenin	
Elaeagnnaceae	*Elaeagnus viridus*		
Ephedraceae	*Ephedera sinica*	Alkaloids: (-) ephedrine, (+) pseudoephedrine, (-) norpseudoephedrine, (+) norephedrine, (-) N-methylephedrine, (+) N-methylpseudoephedrine, ephedradines A,B,C; essential oils: 1-α-terpinol, nonacosan-10-ol, tricosan-1-ol, nonacosane	
Equisetaceae	*Equisetum hyemale*	Palustrine, dimethylsulfone, thymine, ferulic acid, caffeic acid, vanillin, aconitic acid, herbacetin-3-β-D(2-O-β-D-gluco-pyranosidoglucopyranoside)-8-β-D-gluco-pyranoside, gossypetin-3-β-D(2-O-β-D-glucopyranosidoglucopyrano-side)-8-β-D-glucopyranoside	
	Equisetum ramosissimum	Kaempferol-3-sophoroside, kaempferol-3-sophoroside-7-glucoside	[Diuretic] (+)
Euphorbiaceae	*Euphorbia antiquorum*	Firedelaun-3α-ol, α-taxaxerol, β-amyrin, cycloarternol, euphol, α-euphorbol	[Diuretic]
Gentianaceae	*Crawfurdia fasciculuta*		
	Gentianna macrophylla	Gentiopicroside, gentianines A, B, C, gentianidine, gentianol	

(To be continued)

Family name	Latin name	Ingredient	(Liver protection) (+) [Comments]
Gramineae	*Aneurolepidium dasystuchys*		
	Ergrostis pilosa		
	Imperata cylindrica	Anemonin, coxiol, arundoin, cylindrin	[Diuretic]
	Imperata cylindrica var koenigii	Malic acid, citric acid, cylindrin, isoarborinol	
	Lophatherum gracile	Arundoin, cylindrin	
	Melica scabrosa		(+)
	Phyllostachys nigra		
	Pogonatherum crinitum	Flavonoid glycosides, phenols, amino acids, carbohydrates, organic acids	(+)
	Zea mays	Alkaloids, cryptoxanthin, vitmin. K, zeaxanthin, N-ferulyltryptamine, N-(p-coumaryl)-tryptamine, 2"-O- α -L-rhamnosyl-6-c-(6-deoxyxylohexos-4-ulosyl)apigenin, 2"-O- α -L-rhamnosyl-6-c-(6-deoxyxylohexos-4-ulosyl)chrysaeriol, cyclosadol, 24-methyl-*E*-23-dehydrolophenol, 24-methyl-*E*-23-dehydro-cholester (in germ oil)	(+)
	(dried style and stigma)	Glucoside, saponin, fat, essential oil, crystoxanthin, vitamin C & K	[Diuretic & anti-hypertensive] [Treats jaundice, chronic cholecystitis with gallstone]
Juncaceae	*Juncus effusus*	Effusol, β -sitosterol, β -sitosterol- β -D-glucoside	
	Juncus setchuensis var effusoides		
Junglandaceae	*Juglans regia*	Juglone, 3,3'-bisjuglone, cyclotrijuglone (tris-juglone), aricularin (quercetiin-3-arabinoside), hyperin	
Labiatae	*Clerodendranthus spicatus*	Myoinositol, volatile oil	
	Elsholtzia blanda		(+)
	Glechoma longituba		
	Gomphostemma microdon		
	Lamium barbatum	Stachyoseglucoside	(+)
	Leonurus heterophyllus	Alkaloids, flavonoids	
	Ocimum basilicum	Esdragol, methylcinamate, ocimene	
	Scutellaria baicalensis	Baicalein, baicalin, wogonin, wogonoside, neobaicalein(flavones); oroxylin-A, oroxylinA-glucuronide, 7-O-methylwogonin, skullcapflavone Ⅰ, Ⅱ; carthamidin, koganebananin, isocarthamidin, chrysin, baicalin methylester, wogonin-5- β -D-gluco-side, 5,7,2', 6'-tetrahydroxyflavone; 2',5,8-trihydroxy-7-methoxyl-flavone; 2',5,8-trihydroxy-6,7-dimethoxylflavone, dihydro-oroxyin-A, 2(S), 2',5,6'-7-tetrahydroxyflavanone, (2R,3R) -2',3,5,6,7-pentahydroxyflavanone, 2-(3-hydroxy-4-methoxy-phenyl)ethyl-1,0- α -L-rhamnosyl(1→3)- β -D-(4-feruloyl)-glucoside	(+)
Lardizabalaceae	*Akebia quinata*	Oleanolic acid & hederagenin-3-O- β -(sugar)$_n$pyranosides (n=1−5), aristolochic acid, akebin [a saponin]	[Renal toxic] (+) [Diuretic]
Lauraceae	*Cassytha filiformis*	Cassyfiline	(+)
	Cinnamomum cassia	Essential oil: cinnamaldehyde	[↑ Circulation] (+)
	C. obtussifolium	O-methoxycinamaldehyde, cinnamylacetate, phenyl-propyl-acetate, diterpenoids: cinnacassiol A, cinnacassiol A-19-glucoside, cinnzeylanol, cinnzeylanin, D-glucose, D-fructoze, sucrose, tannin	
	Cinnamomum zeylanicum	Eugenol, l-phellandrene, α -pinene	[↑ Circulation]
	Lespedez cuneata	Juglanin, avicularin (quercetin-3-arabinoside), stizolamine, isovitexin, 6,8-di-c-pentosylapigenin, isoorientin, lucenin-2	

(To be continued)

Family name	Latin name	Ingredient	(Liver protection) (+) [Comments]
Leguminosae	*Campylotropis trigonoclada*		
	Cassia nomame		
	Christia obcordata		
	Crotalaria ferruginea	Alkaloids	
	Derris eriocarpa		
	Desmodium styracifolium		
	Desmodium triquetrum		
	Glycyrrhiza uralensis	Saponins: glycyrrhizine→glycyrrhotic acid + glucuronic acid, glabric acid, gerbrolide, 28-hydroxyglycyrrhetic acid; glucose, flavonoids: liquiritin, isoliquiritin, licoflavone, licoricone, liq-uiritigenin, 2-methyl-7-hydroxyisoflavone, licoricidin, amino acids, sucrose, mannitol, asparanic acid, glycerol, isoglycerol	(+)
	Lespedez cuneata	Juglanin, avicularin (quercetin-3-arabinoside), stizolamine, isovitexin, 6,8-di-c-pentosylapigenin	
	Moghania philippinensis		
	Trigonella foenum -gracecum	Gentiamine, carpine, choline, trigonelline, diosgenin, gitogenin yamogenin, β-carotene, tigogenin, vitexin, orientin, quercetin, luteolin, vitamin B1 & C, galactomannan	
Lemnaceae	*Spirodela polyrrhiza*	Potassium acetate, KCl, I_2, flavonoids	[Diuretic] [treats nephritis & measles]
Liliaceae	*Reineckea carnea*	Diosgenin	
	Similax glabra	Alkaloids, phytosterol, linoleic acid, oleic acid	
Lobariaceae (Stictaceae, ascolichene)	*Lobaria pulmonavia*	Hydrocarbon(C_{25}-C_{31}), various fatty acids, palmitic acid, linoleic acid, linolenic acid, ergosterol, fecosterol	
Lycopodiaceae	*Lycopodium clavatum*	Lycopodine, clavatine, clavolonine, fawcetine, acetylfawcetine, fawcetimine	[Diuretic]
Magnoliaceae	*Kadsura coccine*		
	Schisandra chinensis	Tannins, Wuweizisu C, citral, gomisin A, B, C, D, E, F, G, H, J, N, O, R; schisandrin A, C, D, E, γ-schisandrin, deoxyschisandrin, fumaric acid, pregomisin, schizandrol, schisantherin A, C, D, (-) gomisin L_1, L_2, K_1, (+) gomisin K_2, K_3, M_2, (±) gomisin M1, angeloylgomisin H, O, P, Q, tigloylgomisin H & P, benzoylgom-isin H, epigomisin O, sesquicarene, (+) - α-ylangene, yhamigre-nal, α & β-chamigrene, angeloylisogomisin O, d-epigalbacine	(+)
	Schisandra micrantha		
Malvaceae	*Malva neglata*	Fatty acids, resin, mucilage	
	Urena lobata		
Marattiaceae	*Angiopteris magna*		
Marsiliaceae	*Marsilea quadrifolia*		
	Spirodela polyrrhiza		
Melastomataceae	*Melastoma dodecandrum*		
Menispermaceae	*Cocculus tribobus*	Daphnoline, coclobine, trilobine, isotrilobine, magnoflorine, dihydroerysovine, cocculidine, coccutrine, cocculine	
	Stephania cepharantha	Cepharanthine, isotetrandrine, cycleanine, berbamine, quinine, homoaromoline, tetrandrine, papaverine, cepharamine, cepharan-oline, trilobine, codeine, liriodenine, cepharanone A, B, morphine, lysicamine, cepharadione A, B; O-nornuciferine, stephanine, stesakine, crebanine, dehydrocrebanine, berberine	(+)
Moraceae	*Humulus scandens*		
Myrsinaceae	*Ardisia crispa*	Alkaloids, bergenin, ardisic acid	
	Ardisia japonica	Bergenin, ardisin, quercitrin, ardisinol Ⅰ & Ⅱ, myricitrin, ilexol, embelin	
Myrtaceace	*Eucalyptus robusta*		
Myctaginaceae	*Mirabilis himaliaica*		

(To be continued)

Family name	Latin name	Ingredient	(Liver protection) (+) [Comments]
Oleaceae	*Forsythia suspensa*	Saponins, alkaloids, matairesinoside, arctiin (arctin), oleanolic acid, phillygenin, phillyrin, (+)-pinoresinol, (+)-pinoresinol-β-D-glucoside, rutin, forsythid, forsythid-dimethylester, ursolic acid, betulinic acid (betulic acid)	
	Jasminum laurifolium		
Orchidaceae	*Anectochilus taiwanensis*		
	Habenaria delavayi		
	Sarcanthus scolopendrifolius		
	Stayrium nepalense		
Oxalidaceae	*Oxalis griffithii*		
Pandanaceae	*Pandanus furcatus*		(+)
	Pandanus tectorius	Phenols, amino acids, sugars, volatile oil, citral, dipentene, d-linalool, phenyl-ethylacetate, stearoptene ester of phthalic acid	(+)
Papaveraceae	*Corydalis bungeana*	Alkaloids, lactones of coumarin, steroid, saponin, phenols, resin, volatile oil	(+)
	Meconopsis punicea		
Phytolacaceae	*Phytolacca acinosa*	Phytolaccine, saponin, n-pentacosane, 16-hentriacontanol, myristic acid, lignocerylpalmitate, ursolic acid, ursolic acid galactoside, phytolaccanol, epiacetyl aleuritolic acid	
	Phytolacca americcana	Phytolaccatoxin, xanthomicrol, americanins B, D, phytolaccagenin, astragalin, phytolaccoside B, isoquercitrin, phytolaccasaponins B,E G; betanin, oleanolic acid, acetyl aleuritolic acid, acetyl oleanolic acid, phytolaccagenic acid, jaligonic acid	
Piperaceae	*Piper nigrum*	Dihydrocarveol, caryophyllene oxide, piperine, chavicine, piperamine, piperonal, cryptone, trans-pinocarveol	
Plantaginaceae	*Plantago asiatica*	Mucilage, aucubin, choline, adenine, fatty acids: palmitic acid, stearic acid, arachidic acid, oleic acid, linolic acid, succinic acid	[Diuretic]
Plumbaginaceae	*Limonium bicolor*		
Polygonaceae	*Polygonum aviculare*	Avicularin, caffeic acid, vitamin E	[Diuretic]
	Polygonum capitatum		
	Polygonum multiflorum	Anthraquinones: chrysophanic acid, chrysophanol, emodin, rhein, chrysophanic acid, anthrone, lethicin	(+)
	Polygonum perfoliatum	Flavonoids, cardiac glycoside	
Polypodiaceae	*Lepisorus waltonii*		
	Pyrrosia lingua	b-Diploptene, saponin, quinone, β-sitosterol, (-)isomangiferin	
Polyporaceae	*Fomes officinalis*	Eburicoic acid, ergosterol, agaric acid, officinalic acid	
	Polyporus umbellatos	Ergosterol, biotin, gluctan, protein, polysaccharide, 2-hydroxy-tetracosanoic acid	[Diuretic]
	Poria cocos	Polysaccharides: pachyman, ergosterol, eburicoic acid, pachymic acid, tumulosic acid, 3-β hydroxylanosta-7, 9, (11), 24-trien-21-oic acid, hyerin	[Diuretic]
Portulacaceae	*Portulaca oleraceae*		
Primulaceae	*Lysimachia christinae*	Essential oil, l-menthone, l-pinocamphone, l-pinene, limonene, 1,8-cineol, p-cymen	[Diuretic] (+)
Pteridaceae	*Pteris nervosa*		
Ranunculaceae	*Aconitum naviculare*		(+)
	Anemone davidii		(+)
	Clematis armandi	Aristolochic acid, akebin (a saponin), oleanolic acid, akbigin, hederagonin	[Nephrotoxic]
	Clematis chrysocoma		
	Clematis laureiriana		
	Clematis montana	Aristolochic acid, akebin (a saponin), akebigin, hederagonin, oleanolic acid	[Nephrotoxic]
	Paeonoia moutan	Paeonolide, paeonoside, paeoniflorin, oxypaeoniflorin, benzoyl-paeoniflorin, benzoyloxypaeoniflorin, benzoic acid, campsterol, β-sistoterol	[↑ Blood circulation]

(To be continued)

Family Name	Latin Name	Ingredient	(Liver protection) (+) [Comments]
Rhamnaceae	*Berchemia floribunda var mega ophylla*		
	Zizyphus jujuba	Fructose, glucose, sucrose, maleic acid, tartaric acid, oleanolic acid, oleanonic acid, maslinic acid, 3-p-coumaroylate, betulonic acid, betulinic acid, alphitolic acid, ursolic acid, zizyphus saponins Ⅰ, Ⅱ, Ⅲ, jujuboside B, rutin, scopoletin	(+)
Rosaceae	*Rosa multiflora*	Rutin, lycopene, α-carotene, multiflorin A, B, astragalin, 3-rhamnoglucosylkaempferol, quercitrin, multinoside A, B; afzelin, methylgallate, tormentic acid, salicylic acid,gallic acid, 6,7-dimethylesculetin, cholesterol, campsterol, 5-α-stigmastan-3,6-dione	
	Rubus parvifolius	Flavonoid glycosides, tannin, carbohydrate	
Rubiaceae	*Gardenia jasminoides*	Crocin-1, genipin, gentiobioside, gardenoside, gardenin, β-sitosterol, mannitol, tannin, pectin, picrocrocinic acid	(+)
	Gradenia jasminoides Ellis forma grandiflora	Picrocrocinic acid, geniposidic acid, geniposide, 10-acetylgeniposide, gardoside, scandoside methyl ester, shanzhiside, nonacosane, picrocrocinic acid	
	Rubia yunnanensis		
	Schizomussaenda dehiscens		
Rutaceae	*Agathosma betulina*		
	Citrus grandis	Neohesperidin, naringin	
	Zanthoxylum avicennae	Sterols, phenols, organic acids, avicine, hesperidin, diosin, avicennin, candicine, temb-etarine, magnoflorine, chelerythine, avicennol, diosmin, diosmetin	(+)
Salicaceae	*Populus bonatii*		
Schizaeaceae	*Lycopodium fluexuosum*		
	Lycopodium japonicum	Lygodin	(+)
Scrophulariaceae	*Lindernia crustaceae*		
	Rehmannia glutinosa	Catalpol, stachyose, D-glucose, D-galactose, D-fructose, sucrose, raffinose, manninotriose, verbascose, mannitol, β-sitosterol, vitamin A, aucubin, melittoside	(+)
	Siphonotegia chinensis	Cardiac glycoside, volatile oil	(+)
	Striga masuria		(+)
	Veronicastrum axillare	Sterol, mannitol, tannin, resin	(+)
Solanaceae	*Solanum nigrum*	Vitamin A & C; glycoprotein, desgalactotigonin, solasonine, solasodine, solamargine, α-solanine, 26-O-(β-O-ucopyranosyl)-22-methoxy-25D-5α-frost-3β, 26-diol-3-O-β-lycotetraoside	
	Solanum pseudocapsicum		
Symplocaceae	*Symplocos chinensis*		
Taxaceae	*Taxus cuspidata*	Diterpene, taxinine, ponasterone A, ecdysterone, sciadopitysin, taxine, taxol, taxusin, taxa-4(16),11-diene-5,9,10,13-tetraol, taxa-4(20),11-diene-5,9,10,13-tetraol-9,11-di-O-acetate; taxa-4(20), 11-diene-2,5,7,10-tetraol-2-(α-methylbutylroyl)-5,7,10-tri-O-acetate; taxa-4(20),11-diene-2,5,7,9,10-pentaolol-2-i-butyroyl-7,9,10-tri-O-acetate; taxa-4(20),11-diene-2,5,7,9,10-pentaolol-2-i-butyroyl-5,7, 9,10-tetra-O-acetate; taxa-4(20), 11-diene-5,7,9, 10,13-pentaol-penta-O-acetate, taxa-4(20),11-diene-2,5,7,9,10, 13-hexol-hexa-O-acetate; taxinine, taxinine A,H,K,L; taxisterone	
Umbelliferae	*Angelica sinensis*	Essential oil: ligustilide, n-butylidenphthalide, n-butyl phthalide, n-valerophenone-O-carbonic acid, sedanoic acid, safrol, isosafrol, p-cymene, carvacrol; fatty acids: palmitic acid, linolic acid, stearic acid, arachidonic acid; coummarins: bergaptene, biotin scopoletin, umbelliferone, falcarinol, falcarindiol, falcarindone, n-dodecanol, β-sitosterol, β-sitosterol glucoside, glucose, folic acid, fructose, sucrose, vanillic acid, nicotinic acid, nicotinamide, pantothenic acid, folinic acid, vitamin B_{12}, biotin	[Diuretic] (+)
	Bupleurum chinensis	Oleic acid, linoleic acid, linolenic acid, saikosaponins a, b, c, d; saikogenins E,F,G; sterols: α-spinasterol, stigmasterol, Δ^7-stigma-sterol, Δ^{22}-stigmastenol, sugar: adonitol	(+)

(To be continued)

Family name	Latin name	Ingredient	(Liver protection) (+) [Comments]
Umbelliferae	*Hydrocotyle sibthorpioides*	Quercetin, hyperin, isorhamnetin, volatile oil, coumarin, hyperoside, phenols, amino acids	(+)
	Ligusticum chuanxiong	Essential oils: ligustilide, butylidenphthalide, butylphthalide, neocnidilide, cnidilide, sedanolide, senkyunolide, ferulic acid, cnidium lactone, D-glucose, D-fructose, sucrose, amino acids, oil-like alkaloids	[Vasodilating]
Verbenaceae	*Caryopteris incana*		
Violaceae	*Viola dissecta*		
	Viola yedoensis	Flavonoids, cerotic acid	
Vitaceae	*Ampelopsis brevipedum-culata*		
	Ampelopsis cantoniensis		
	Cissus modecoides		
Zingiberaceae	*Zingiber officinale*	Essential oils: zingiberene, bisabolene, camphene, α -pinene, cineol, β -phellandrene, myrcene; pungent components: gingerol, zingerone, shogaol	
Minerals	*Talcum depuratum*	Clacium carbonate	
	Magnesium chloride	$MgCl_2$ crystals	
Animals	*Cipangopaludina chinensis*	Vitamin A	
	Capra hircus	Proteins, fatty acids	
	Carassius auratus	Carotenoids, lutein, xanthophll, astaxathin, ketolutein, 4,4'-diketo-3-hydroxy- β -carotene	

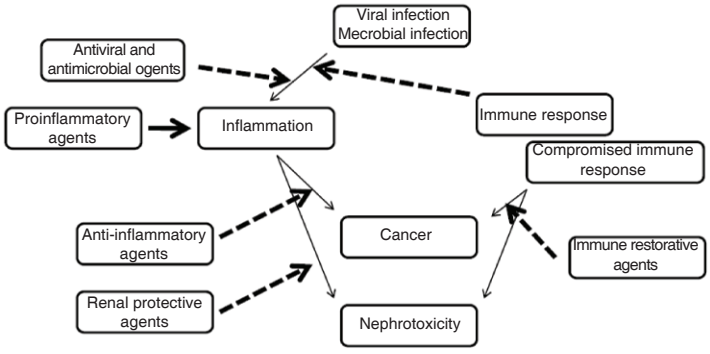


Figure 1. The Interplay among Proinflammatory, Anti-Inflammatory, Renal Protective Agents and Immune Response

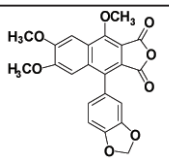
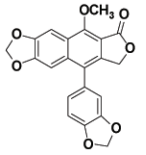
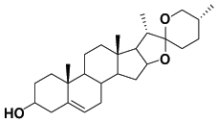
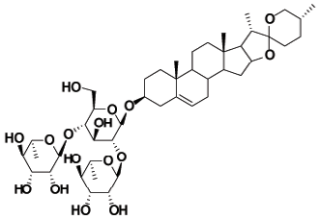
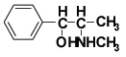
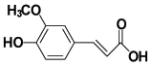
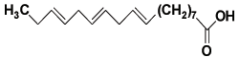
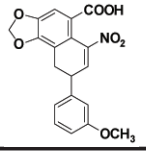
Note: the heavy arrow indicates stimulation and dashed heavy arrows show blockade

of action. The most striking case is the presence of nephrotoxic compound aristolochic acid in two of the nephropretective herbs, *Akebia quinata* and *Aristolochia manshuriensis*. The nephrotoxicity may be due to dose, length of exposure or the presence of other compounds resulting in enhanced toxicity. In terms of structure, aristolochic acid is an aromatic acid with a nitro group attached to the neighboring ring. Many nitro compounds are known to have a wide range of activities and toxicities. The exact mechanism remains to be examined.

Future Research Directions

There are two entirely different approaches in the future research on TCM. The first one may be called a "sharp shooter" approach. That is to select a particular plant with a specific activity or a biological target. By using bioactivity-guided isolation and structural elucidation, one can discover a new chemical entity for a specific disease, such as turning on and off a specific gene involved in a disease state (epigenetic). The second approach is like a "shotgun" approach. Instead of targeting a specific receptor or mechanism, one can select proper combinations of herbs or ingredients, and optimize the outcome of treatment by different combinations and dose regimens. In this approach it is not necessary to identify the exact active ingredient(s), but it is still necessary to have quality control of the preparations to ensure reproducibility. One can select certain chemical markers in the preparations as well as standardize the raw materials and processing procedures. Once a

Table 2. Representative Structures of Kidney Protective/toxic Compounds1-4, 24 and Their Key Physico-Chemical Parameters ([a]MW, [b]Clog P, [b]CMR, [c] μ and [c]E_{lumo})

Source	Compound name	Structure	Comment
Rostellularia procumbens	Justicidin C MW = 408.36; Clog P=4.45; CMR=10.31 μ = 7.96; E_{lumo}= −1.32		Lignan of phenyltetraline type
	Justicidin D MW = 378.33; ClogP=3.95; CMR=9.63 μ = 4.84; E_{lumo}= −1.12		Lignan of phenyltetraline type
Dioscoria sativa *Dioscoria tokoro*	Diosgenin MW = 414.62; Clog P=5.91; CMR=12.07 μ = 3.07; Elumo= 1.25		Aglycone, lipophilic
	Dioscin MW =869.04; ClogP=0.59; CMR=21.88 μ = 3.48; E_{lumo}= 1.13		A glycoside
Ephdra sinica	*l*-Ephedrine MW =165.23; ClogP=0.89; CMR=5.07 μ = 2.51; E_{lumo}= 0.46		An alkaloid sympatho-mimetic
Ligusticun chuaxion *Catalpa ovate*	Ferulic acid MW =194.18; ClogP=1.42; CMR=5.32 μ = 3.59; E_{lumo}= −0.80		Antioxidants
Lobaria pulmonavia	Linolenic acid MW =278.43; ClogP=6.82; CMR=8.64 μ = 1.86; E_{lumo}= 1.02		Antioxidants
Akebia quinata *Aristolochia manshu-riensis*	Aristolochic acid; MW = 369.32; ClogP=1.26; CMR= 9.58 μ = 6.43; E_{lumo}= −1.21		A nephrotoxic aromatic acid with a nitro a group

Notes: a: calculated from the structures by ChemBioDraw Ultra 12.0; b: calculated by using ChemBio 3D Ultra; c: calculated from HyperChem 8.0 program after performing geometry optimization and energy minimization using AM1 semiempirical method, and using the Polak-Riviere conjugate gradient with RHF spin pairing, 0.01 convergence limit in vacuum and RMS gradient of kcal/(Åmol).

reproducible preparation is obtained and its biological activity is established, it can be used to treat certain given disease in the general patient population. A good example would be immune modulators used to enhance compromised immune system[22,23] or to soften overreaction of the immune system.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Lien EJ and Lien LL contributed equally in the literature survey, compilation and interpretation. Wang R compiled Tables 1 and 2, and the computation of the physicochemical parameters used in Table 2. Wang J contributed to the drawing of Figure 1 and the editing of the manuscript.

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(Received September 4, 2010)
Edited by YUAN Lin