Nephroprotective Effect of *Panax Ginseng*: A Systematic Review of Preclinical Studies in Animals

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Abstract

Introduction: Our objective was to shed light to the in vivo nephroprotective activity of *Panax ginseng* in animal models.
Methodology: Systematic review in which the databases Medline (PubMed), Web of Science, Embase and Virtual Health Library were used to search for articles. The eligibility criteria were preclinical in vivo trials that evaluated the nephroprotective effect of *P. ginseng* by dosing biochemical markers in serum or urine.
Results: Forty-five controlled pre-clinical trials were included. Among the 16 studies that employed the animal model of diabetes kidney disease, 14 observed a nephroprotective effect of *P. ginseng* derivatives. All 30 studies employing animal models of kidney injury induced by drugs or nephrotoxic substances or caused by ischemia-reperfusion found *P. ginseng* to have a nephroprotective effect.
Conclusion: The *P. ginseng* shows remarkable nephroprotective effects in different animal models of nephropathy. Therefore, its use is promising as an adjuvant in the treatment of diabetes kidney disease and prevention of drug-induced nephropathy. Further randomized controlled clinical trials in humans are required to validate these findings.

Keywords: Acute Kidney Injury; Animals; Diabetic Nephropathies; Drug-Related Side Effects and Adverse Reactions; Panax; Renal Insufficiency, Chronic

INTRODUCTION

Panax ginseng belongs to the *Araliaceae* family, and its name refers to a plant that "treats all diseases". It is commonly used in Korea, China and Japan; however, its use has also been highlighted worldwide, owing to its great therapeutic potential as adaptogenic.[1]

Popularly known as ginseng, this plant can be divided into three categories based on processing technologies, i.e., fresh, white and red ginseng.[2] It has a wide range of phytochemicals, with ginsenosides (saponins) being the main active constituents. Polysaccharides account for about 40% of the compounds. In addition to these the plant contains alkaloids (β-carboline), glycosides, phenolic acid, and others.[3]

The *P. ginseng* has shown great potential in protecting kidney cells due to the high antioxidant and free radical scavenging power of ginsenosides.[4] Diabetes kidney disease (DKD) is one of the main underlying diseases of chronic kidney disease (CKD).[5] Sodium-glucose cotransporter-2 (SGLT2) inhibitors hypoglycemic drugs and antihypertensives from the angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) classes can be used in the treatment of DKD, as they can slow or prevent disease progression in many patients, but do not have the ability to prevent it.[6,7]

Hence, there are still great challenges in the treatment of patients with DKD, and the study of new drugs is of utmost importance. The possibility of using *P. ginseng* as an adjuvant in treating and preventing DKD raises the chances of great advances in the early approach to the patient with DKD.[5,8] In addition, there are reports of its beneficial effect on acute kidney injury and renal senescence.[4]

Another possibility of kidney protection by *P. ginseng* would be reached when it is imperative to use drugs known to be nephrotoxic, such as aminoglycosides, amphotericin B, polymyxins and cisplatin, which even in

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therapeutic doses, can compromise the functionality of the kidneys. Hence, the *P. ginseng* can mitigate such undesirable effects.[4]

Seeking to contribute to the rationale use of *P. ginseng* in phytotherapy, we report on a systematic review shedding light on the significant nephroprotective activity of *P. ginseng* in controlled preclinical trials performed in animal models.

METHODS

Study design

We performed a systematic review according to the *Preferred Reporting Items for Systematic reviews and Meta-Analyses* (PRISMA)[9] statement. The review was not registered and a protocol was not prepared.

Search strategy

To identify preclinical trials involving the use of *P. ginseng* derivatives in the treatment of DKD, systematic literature searches were performed in the following electronic databases Medline (PubMed), Web of Science, Embase and the Virtual Health Library. The search terms were combined using the Boolean logical terms "AND" and "OR". The complete search strategy is showcased in the Supplementary Material. Reference lists of the included studies and reviews were also examined for additional eligible studies not recovered by the research.

The search for articles in the databases was conducted until March 3, 2022. There was no restriction as to the date of publication of the articles, nor as to the language. The authors of the unavailable articles were contacted at least twice via e-mail requesting access to their work.

Eligibility criteria

Preclinical in vivo trials evaluating the nephroprotective effect of *P. ginseng* were defined as eligibility criteria. Eligibility criteria were established according to PRISMA recommendations.[9] Articles that evaluated the use of *P. ginseng* in combination with other substances were excluded.

Only studies whose experimental design allowed the following points to be distinguished, according to the acronym PICOS, were included in the systematic review:

- Population: Animals with CKD, DKD, hypertensive nephropathy, acute kidney injury, or drug-induced kidney injury that received *P. ginseng*.
- Intervention: Administration of *P. ginseng* in any dose, route and frequency.
- Control: Animals with CKD, DKD, hypertensive nephropathy, acute kidney injury, or drug-induced kidney injury that did not receive *P. ginseng*.
- Outcome: Nephroprotective effect evidenced by one or more of the following markers: serum creatinine, serum urea, creatinine clearance, glomerular filtration rate, albuminuria, and proteinuria.
- Study design: *in vivo* controlled preclinical trial.

Article selection

The selection of the articles was performed in two steps, both carried out by two authors independently. Disagreements were resolved by a third author. First, the repeated articles were excluded, and then, a preliminary reading of the title and abstract of the articles was performed in order to include only those that are pre-clinical trials *in vivo* and that evaluate the nephroprotective effect of *P. ginseng* evidenced by one or more of the following markers: serum creatinine, serum urea, creatinine clearance, glomerular filtration rate, albuminuria, proteinuria. Afterward, the pre-selected articles were read in their entirety to assess their inclusion in the study according to the eligibility criteria.

Data extraction

Data extraction was performed by two authors independently. Disagreements were resolved by a third author. The following data were extracted from the selected articles for the construction of tables: active components of *P. ginseng*; part of the plant used; dose administered of *P ginseng*; route of administration; duration of treatment; type of animal strain; sample size of the intervention group and control group; type of animal model of nephropathy; method of nephropathy induction; biochemical markers used to evaluate the nephroprotective effect; result obtained.

Risk of bias assessment

The methodological quality of the studies included in the systematic review was independently assessed by two people using the SYRCLE tool,[10] which assesses the risk of bias for animal studies. Disagreements were resolved by a third author. This tool contains the following assessment categories: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. Ten questions are applied to the articles included in the systematic review, the answers to which can be "YES" indicating low risk of bias, "NO" indicating high risk of bias, and "UNCERTAIN" indicating uncertain risk of bias. It is not recommended that the sum score of each individual study be calculated using this tool.[9]

RESULTS

Fig. 1 depicts the article selection steps. After the evaluation of the eligibility criteria, 45 studies were included in the systematic review.

Table 1 shows the characteristics of the preclinical studies included in the systematic review, which were published between the years 2000 and 2021. The doses employed for the different components of *P. ginseng* ranged from 1 to 800 mg/kg, the duration of treatment ranged from five to eighty-four days, with control and intervention group sizes ranging from four to seventeen animals.

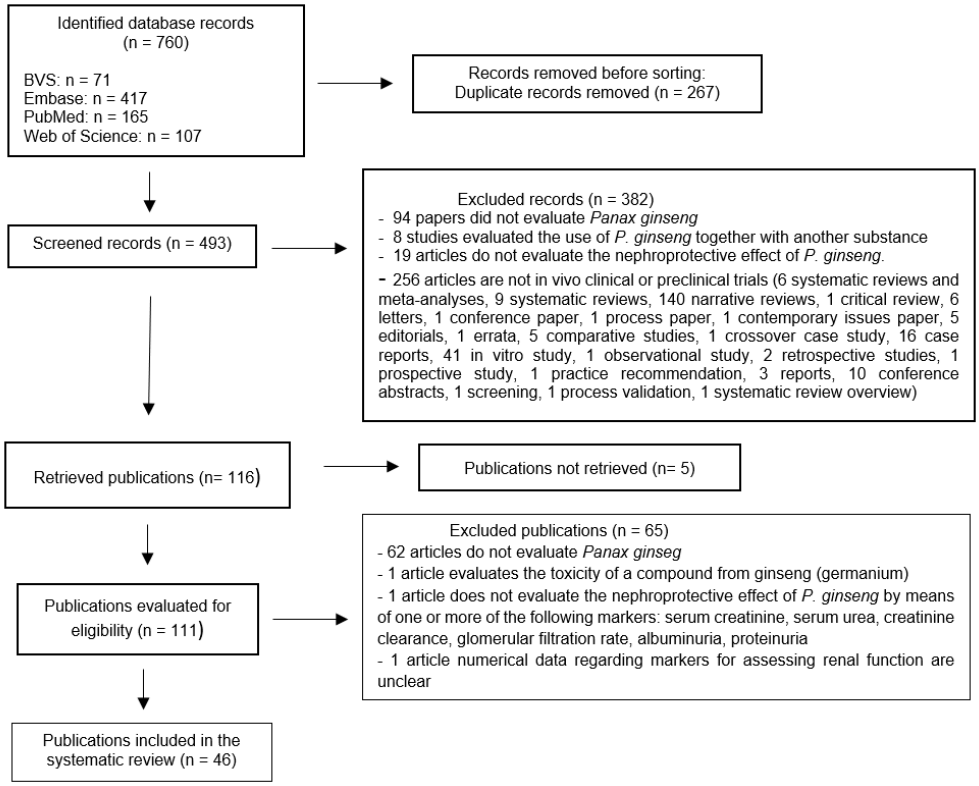

Figure 1. Flowchart of the selection of articles that evaluated the nephroprotective effect of *Panax ginseng* and were included in the systematic review.

Table 1. Summary of the features of the preclinical studies that evaluated the nephroprotective effect of *Panax ginseng* and were included in the systematic review

Author, year	Ginseng derivative	Part of the plant used	Dose administered/route of administration	Treatment duration	Animal strain	Intervention and control group size
Zhu *et al.*, 2020[23]	ginsenoside Rg5	NI	30 and 60 mg/kg/ Oral	35 days	male C57BL/6 mice	05/05
Huang *et al.*, 2018[24]	polysaccharide	NI	25, 50 and 100 mg/kg/ Oral	84 days	male C57BL/6 mice	10/10
Li *et al.*, 2021[51]	ginsenoside 20(R)Rg3	roots	10 and 20 mg/kg/ Intragastric	56 days	adult male C57BL/6 mice	10/10
Su *et al.*, 2021[25]	ginsenoside Rh1	NI	5 and 10 mg/kg/ Oral	56 days	C57BL/6 mice	10/10
Jung *et al.*, 2021[26]	crude extract modified with pectin-lyase and ginsenoside Rd	NI	100 and 250 mg/kg/ Oral	42 days	male db/db mice	08/08
Kang *et al.*, 2010[27]	crude extract and ginsenoside 20(S)-Rg3	NI	5, 10 and 100 mg/kg/ Oral	50 days	male Otsuka Long-Evans Tokushima rats	09/09
Quan *et al.*, 2013[28]	crude extract	NI	100 and 250 mg/kg/ Oral	28 days	SD rats	04/04
Kim *et al.*, 2017[11]	GS-E3D extract	NI	25, 50 and 100 mg/kg/ Oral	42 days	male Sprague--Dawley rats	10/10
Karunasagara *et al.*, 2020[12]	crude extract	roots	250 and 500 mg/kg/ Oral	28 days	male Sprague--Dawley rats	06/06
Shi *et al.*, 2020[13]	ginsenoside Rg1	NI	50 mg/kg/ Intraperitoneal	56 days	male Sprague--Dawley rats degree SPF	08/08
Kang *et al.*, 2006[29]	crude extract	NI	50 and 100 mg/kg/ Oral	15 days	male Wistar rats	08/08

Author, year	Ginseng derivative	Part of the plant used	Dose administered/route of administration	Treatment duration	Animal strain	Intervention and control group size
Kim *et al.*, 2008[30]	Crude extract	NI	100 mg/kg/ Oral	20 days	male Wistar rats	08/08
Wang *et al.*, 2021[44]	ginsenoside Re	NI	25 mg/kg/ Intragastric	30 days	male Wistar rats	06/08
Kang *et al.*, 2008[31]	maltol	NI	10, 20 and 50 mg/kg/ Oral	15 days	male Wistar rats	07/07
Kang *et al.*, 2008[32]	maltol	NI	5, 10 and 20 mg/kg/ Oral	15 days	male Wistar rats	08/08
Shao *et al.*, 2015[54]	ginsenoside Rb1 após transformação pela β-glicosidase	roots	5 and 10 mg/kg/ Intragastric	49 days	male Wistar rats	08/08
Qi *et al.*, 2017[40]	crude extract	fruits	200 and 400 mg/kg/ Intragastric	10 days	male ICR mice	08/08
Li *et al.*, 2019[45]	arginil-frutosil-glicose	NI	40 and 80 mg/kg/ Intragastric	10 days	male ICR mice	10/10
Wei *et al.*, 2021[52]	polysaccharide	roots	200 and 400 mg/kg/ Intragastric	10 days	male ICR mice	08/08
Li *et al.*, 2016[55]	ginsenoside Rg5	bark/leaves	11 and 20 mg/kg/ Intragastric	10 days	male ICR mice	08/08
Kim *et al.*, 2014[14]	crude extract	roots	100, 300 and 500 mg/kg/ Oral	28 days	male Sprague--Dawley rats	06/06
Baek *et al.*, 2017[15]	ginsenosides Rk3 and Rh4	roots	2 and 6 mg/kg/ Oral	5 days	male Sprague--Dawley rats	06/06
Yokozawa *et al.*, 2000[33]	ginsenoside Rd	NI	1 and 5 mg/kg/ Oral	30 days	male Wistar rats	NI
Jung *et al.*, 2017[34]	crude extract	NI	150 mg/kg/ Oral	10 days	male Wistar rats	04/04
Park *et al.*, 2015[35]	crude extract	NI	100 mg/kg/ Oral	10 days	male C57/BL mice	04/04
Zhang *et al.*, 2021[46]	ginsenoside 20(R)Rg3	NI	10 and 20 mg/kg/ NI	10 days	male ICR mice	08/08
Qi *et al.*, 2019[47]	ginsenoside Rh(2)	NI	20 and 40 mg/kg/ Intragastric	10 days	male ICR mice	08/08
Zhai *et al.*, 2021[36]	ginsenoside Rg3	NI	5 mg/kg/ Oral	10 days	Male Kunming mice	10/10
Yousef *et al.*, 2015[16]	crude extract	NI	100 mg/kg/ Oral	15 days	male Sprague--Dawley rats	10/10
Kalkan *et al.*, 2012[17]	crude extract	NI	100 and 200 mg/kg/ Intraperitoneal	10 days	adult male Sprague-Dawley rats	08/08
Lee *et al.*, 2013[18]	crude extract	roots	100 mg/kg/ Oral	28 days	male Sprague--Dawley rats	04/04
Shin *et al.*, 2014[19]	crude extract	roots	100 mg/kg/ Oral	30 days	male Sprague--Dawley rats	16/16
Qadir *et al.*, 2011[37]	crude extract	NI	100 mg/Kg/ Oral	15 days	male albine mice	06/06
Karadeniz *et al.*, 2008[20]	crude extract	NI	200 mg/kg/ Intraperitoneal	10 days	male Sprague--Dawley rats	08/08
Lim *et al.*, 2014[41]	crude extract	NI	200 and 400 mg/kg/ Subcutaneous	28 days	male ICR mice	08/08
Doh et al., 2013[38]	crude extract	NI	200, 400 and 800 mg/kg/ Oral	28 days	male mice	06/06
Fan *et al.*, 2016[48]	ginsenoside Rg1	NI	20 mg/kg/ Intraperitoneal	43 days	MiceC57BL/6 machos	10/10
Li *et al.*, 2020[49]	ginsenoside 20(R)Rg3	NI	10 and 20 mg/kg/ Intragastric	56 days	male ICR mice	08/08
Sun *et al.*, 2013[50]	ginsenoside Rb1	NI	6 mg/mL/ Intraperitoneal	NI	adult male C57BL/6 rats	08/08
Kim *et al.*, 2013[21]	crude extract	NI	25, 50 and 100 mg/kg/ Oral	20 days	male Sprague--Dawley rats	07/07

Author, year	Ginseng derivative	Part of the plant used	Dose administered/route of administration	Treatment duration	Animal strain	Intervention and control group size
Ragab *et al.*, 2021[39]	crude extract	NI	100 mg/kg/ Oral	28 days	female albine rats	10/10
Elblehi *et al.*, 2019[42]	crude extract	NI	200 mg/kg/ Intragastric	30 days	albine male Wistar rats	10/10
El *et al.*, 2016[53]	ginsenoside Rb1	roots	100 mg/kg/ Intragastric	14 days	adult albine male rats Wistar rats	10/10
El *et al.*, 2012[22]	crude extract	NI	20 mg/kg/ Oral	28 days	male Sprague--Dawley rats	10/10
Mansour, 2013[43]	crude extract	NI	100 mg/kg/ Intragastric	7 days	male Wistar rats	06/06

NI= não informado.

The type of mouse and route of administration varied widely among the studies, with the majority[11-22] used Sprague-Dawley rats and the oral route.[11,12,14-19,21-39] The *P. ginseng* derivatives used in the preclinical trials varied among the articles, with the majority using the bulk extract.[12,14,16-22,25,27-30,34-43] The part of the plant used was not reported in thirty-four studies[11,13,16,17,20-39,41-50] (75.56%); nine studies used the root[12,14,15,18,19,51,52,53,54] (20.00%); one study used the stem and leaves[55] (2.22%); and one study used the fruits[40] (2.22%).

Table 2 shows the animal model of nephropathy, the biochemical markers used to evaluate the nephroprotective effect, and the results of the selected preclinical studies. DKD was the animal model of nephropathy most often used by studies[11-13,23-32,44,51,53,54] (n=16, 35.56%). Among the studies using the animal model of DKD, the most used method of inducing diabetes mellitus (DM) was the administration of streptozocin.[11-13,23-25,28-32,44,51,53,54]

Other animal models of nephropathy used were: cisplatin--induced nephropathy (n=13, 28.89%)[14-16,33-36,40,45-47,52,55]; gentamicin-induced nephropathy (n=5, 11,11%)[17-20,37]; cyclosporine-induced nephropathy (n=2, 4.44%)[38,41]; D-galactose-induced nephropathy (n=2, 4.44%)[48,49]; renal injury caused by occlusion of the superior mesenteric artery (n=1, 2.22%)[50]; adenine-induced nephropathy (n=1, 2.22%)[21]; nitroarginine-induced nephropathy (n=1, 2.22%)[39]; hydroxyurea-induced nephropathy (n=1, 2.22%)[42]; lithium--induced nephropathy (n=1, 2.22%)[53]; carbon tetrachloride--induced nephropathy (n=1, 2.22%)[22]; and kidney damage from gamma radiation exposure (n=1, 2.22%)[43].

Of the sixteen studies that used the animal model of DKD, [11-13,23-32,44,51,53,54] ten[13,23,24,28,29,31,40,44,51,54] (62.50%) evaluated serum creatinine levels, and among these, six[13,23,24,29,51,54] (60.00%) observed that creatinine levels decreased after treatment. Eleven studies[12,13,23,24,28,29,31,44,51,53,54] (68.75%) evaluated serum urea levels, among these, nine[12,13,23-25,29,44,51,54] (81.82%) found a reduction in urea levels after treatment. Five studies[11,13,24,26,29] (31.25%) evaluated albuminuria and all[11,13,24,26,29] reported a significant reduction in albuminuria after treatment. Five studies[27,29,30-32] (31.25%), evaluated proteinuria, of which four[27,29,30,32] (80.00%) found a reduction in proteinuria after treatment. Five studies[27,29-32] (31.25%) have evaluated creatinine clearance, among these, three[27,30,32] (60.00%) found an increase in this parameter.

Among the thirteen studies that evaluated cisplatin--induced nephropathy[14-16,33-36,40,45-47,52,55], all evaluated serum creatinine levels, of which twelve[14,15,16,33,35,36,40,45-47,52,55] (92.31%) found a significant reduction in creatinine levels after treatment. Eleven studies[14,15,16,33,36,40,45-47,52,55] (84.62%) have evaluated serum urea levels and all found a reduction in urea levels after treatment. Only one study[34] (7.69%) evaluated creatinine clearance, which increased after treatment.

The five studies that evaluated gentamicin-induced nephropathy,[17-20,37] all evaluated serum urea levels and found a reduction in urea levels at the end of treatment. Four of these studies[17,19,20,37] (80.00%) have evaluated serum creatinine levels and all of them found a reduction in the levels of this marker at the end of treatment. One study[18] (20.00%) assessed creatinine clearance, which increased at the end of treatment.

Both the studies dealing with cyclosporine-induced nephropathy[38,41] evaluated serum creatinine levels and only one[41] (50.00%) found a reduction in creatinine levels after treatment. One study[38] (50.00%) evaluated serum urea levels, which decreased after treatment. One study[38] (50.00%) evaluated creatinine clearance, which increased after treatment. One study[41] (50.00%) evaluated albuminuria and there was no significant difference after treatment.

The two studies evaluating D-galactose-induced nephropathy[48,49] assessed the serum urea levels and found a reduction in urea levels after treatment. One study[48] (50.00%) also evaluated serum creatinine levels, which decreased at the end of treatment.

The studies that have evaluated the renal damage caused by occlusion of the superior mesenteric artery,[50] adenine--induced nephropathy,[21] nitroarginine-induced nephropathy,[39] hydroxyurea-induced nephropathy,[42] carbon tetrachloride nephropathy,[22] the kidney damage caused by exposure to gamma radiation[43] and lithium-induced nephropathy[53] have evaluated the serum levels of urea and creatinine. All of these studies found a reduction in

serum urea and creatinine levels at the end of treatment. The study that evaluated lithium-induced nephropathy[53] also looked at albuminuria and creatinine clearance, and found that albuminuria decreased, while creatinine clearance increased at the end of treatment.

Fig. 2 shows the results of the risk of bias assessment of the articles included according to the SYRCLE.

Table 2. Animal model of nephropathy, biochemical markers used to evaluate the nephroprotective effect, and results of the preclinical studies included in the systematic review.

Author, year	Animal model of nephropathy/ Method of nephropathy induction	Biochemical markers for assessing renal function	Main outcomes
Zhu *et al.*, 2020[23]	DKD/ Streptozocin administration	Serum urea	Lower levels in the group receiving 60 mg/kg of the ginsenoside Rg5 compared to CG ($p < 0.05$)
		Serum creatinine	Lower levels in the groups that received 30 and 60 mg/kg of the ginsenoside Rg5 compared to CG ($p < 0.01$ and $p < 0.001$, respectively)
Huang *et al.*, 2018[24]	DKD/ Streptozocin administration	Serum urea	Lower levels in the groups receiving 25 mg/kg (26.48 ± 1.54 mg/L), 50 mg/kg (25.65 ± 2.48 mg/L) and 100 mg/kg (23.57 ± 2.02 mg/L) of *P. ginseng* polysaccharides compared to CG (32.75 ± 1.76 mg/L) ($p < 0.05$)
		Serum creatinine	Lower levels in the groups receiving 25 mg/kg (0.50 ± 0.09 mg/L), 50 mg/kg (0.45 ± 0.08 mg/L) and 100 mg/kg (0.39 ± 0.07 mg/L) of *P. ginseng* polysaccharides compared to CG (0.69 ± 0.12 mg/L) ($p < 0.05$)
		Albuminuria	Lower levels in the groups receiving 25 mg/kg (7.69 ± 1.82 mg/24h), 50 mg/kg (6.21 ± 0.73 mg/24h) and 100 mg/kg (4.16 ± 0.65 mg/24h) of *P. ginseng* polysaccharides compared to CG (9.74 ± 1.12 mg/24h) ($p < 0.05$)
Li *et al.*, 2021[51]	DKD/ Streptozocin administration	Serum urea	Lower levels in groups receiving 10 and 20 mg/kg of the ginsenoside 20(R)Rg3 compared to CG ($p < 0.05$ and $p < 0.01$, respectively)
		Serum creatinine	Lower levels in the group receiving 20 mg/kg of the ginsenoside 20(R)Rg3 compared to CG ($p < 0.05$)
Su *et al.*, 2021[25]	DKD/ Streptozocin administration	Serum urea	Lower levels in groups receiving 5 and 10 mg/kg of the ginsenoside Rh1 compared with CG ($p < 0.01$)
Jung *et al.*, 2021[26]	DKD/genetically engineered mouse with DM	Albuminuria	Lower levels in the groups receiving 100 and 250 mg/kg of ginseng extract modified with pectin lyase and ginsenoside Rd compared to CG ($p < 0.05$)
Kang *et al.*, 2010[27]	DKD/ Mouse with obesity and T2DM	Proteinuria	Lower levels in the groups that received 10 and 100 mg/kg of the thermally processed ginseng and its active component ginsenoside 20(S)-Rg3 compared to the CG ($p < 0.05$).
		Creatinine clearance	Higher levels in the groups that received 5, 10, and 100 mg/kg of the thermally processed ginseng and its active component ginsenoside 20(S)-Rg3 compared to the CG ($p < 0.05$)
Quan *et al.*, 2013[28]	DKD/ Streptozocin administration	Serum urea	There was no significant difference between the groups that received 100 and 200 mg/kg of *P. ginseng* and the CG
		Serum creatinine	There was no significant difference between the groups that received 100 and 200 mg/kg of *P. ginseng* and the CG
Kim *et al.*, 2017[11]	DKD/ Streptozocin administration	Albuminuria	Lower levels in the groups that received 50 and 100 mg/kg of the GS-E3D extract compared to CG ($p < 0.05$)
Karunasagara *et al.*, 2020[12]	DKD/ Streptozocin administration	Serum urea	Lower levels in the groups that received 250 and 500 mg/kg of *P. ginseng* compared to CG ($p < 0.01$ and $p < 0.001$, respectively)
Shi *et al.*, 2020[13]	DKD/ Streptozocin administration	Serum urea	Lower levels in the group that received 50 mg/kg of the ginsenoside Rg1 compared to CG ($p < 0.01$)
		Serum creatinine	Lower levels in the group that received 50 mg/kg of the ginsenoside Rg1 compared to CG ($p < 0.01$)
		Albuminuria	Lower levels in the group that received 50 mg/kg of *P. ginseng* compared to CG ($p < 0.01$)

Author, year	Animal model of nephropathy/ Method of nephropathy induction	Biochemical markers for assessing renal function	Main outcomes
Kang *et al.*, 2006[29]	DKD/ Streptozocin administration	Serum urea	Lower levels in the group receiving 50 mg/kg of *P. ginseng* (24.5 ± 1.0 mg/dL) compared to CG (26.0 ± 0.6 mg/dL) ($p < 0.05$)
		Serum creatinine	Lower levels in groups receiving 50 mg/kg (0.28 ± 0.01 mg/dL) and 100 mg/kg of *P. ginseng* (0.28 ± 0.01 mg/dL) compared to CG (0.32 ± 0.01 mg/dL) ($p < 0.001$)
		Proteinuria	Lower levels in groups receiving 50 mg/kg (9.9 ± 1.0 mg/dL) and 100 mg/kg of *P. ginseng* (8.9 ± 0.7 mg/dL) compared to CG (13.0 ± 0.6 mg/dL) ($p < 0.001$)
		Albuminuria	Lower levels in the groups that received 50 and 100 mg/kg of *P. ginseng* compared to CG ($p < 0.01$)
		Creatinine clearance	There was no significant difference between the groups that received 50 and 100 mg/kg of *P. ginseng* and the CG
Kim *et al.*, 2008[30]	DKD/ Streptozocin administration	Serum creatinine	There was no significant difference between the group receiving 100 mg/kg *P. ginseng* and the CG
		Proteinuria	Lower levels in the groups that received 100 mg/kg (9.5 ± 0.3 mg/day and 8.8 ± 0.8 mg/day) of the heated and unheated *P. ginseng* extracts respectively compared to the CG (13.1 ± 1.1 mg/day) ($p < 0.05$)
		Creatinine clearance	Higher levels in the group that received 100mg/kg (9.93 ± 0.78 mg/day) of the heated extract of *P. ginseng* compared to the CG (6.89 ± 0.63 mg/day) ($p < 0.05$)
Wang *et al.*, 2021[44]	DKD/ Streptozocin administration	Serum urea	Lower levels in the group receiving 25 mg/kg of the ginsenoside Re (6.61 ± 1.33 mmol/L) compared to the CG (8.75 ± 1.62 mmol/L) ($p < 0.05$)
Kang *et al.*, 2008[31]	DKD/ Streptozocin administration	Serum creatinine	There was no significant difference between the group receiving 10 and 20 mg/kg of maltol and the CG
		Serum urea	There was no significant difference between the group receiving 10 and 20 mg/kg of maltol and the CG
		Creatinine clearance	There was no significant difference between the group receiving 10 and 20 mg/kg of maltol and the CG
		Proteinuria	There was no significant difference between the group receiving 10 and 20 mg/kg of maltol and the CG
Kang *et al.*, 2008[32]	DKD/ Streptozocin administration	Serum creatinine	There was no significant difference between the group receiving 10 and 20 mg/kg of maltol and the CG
		Proteinuria	Lower levels in the group receiving 20 mg/kg (19.4 ± 2.2 mg/day) of maltol compared to CG (28.4 ± 1.3 mg/day) ($p < 0.01$)
		Creatinine clearance	Higher levels in the groups receiving 5 mg/kg (9.27 ± 0.44 mg/dL) ($p < 0.05$), 10 mg/kg (9.65 ± 0.48 mg/dL) ($p < 0.01$) and 20 mg/kg (10.00 ± 0.51 mg/dL) ($p < 0.01$) of maltol compared to CG (7.88 ± 0.41 mg/dL)
Shao *et al.*, 2015[54]	DKD/ Streptozocin administration	Serum urea	Lower levels in the group receiving 10.5 mg/kg (11.3 ± 1.8 mmol/L) of the ginsenoside Rb1 after transformation by β-glucosidase compared to the CG (15.4 ± 51.2 mmol/L) ($p < 0.05$)
		Serum creatinine	Lower levels in the group receiving 10.5 mg/kg (127.1 ± 5.5 µmoL/L) of the ginsenoside Rb1 after transformation by β-glucosidase compared to the CG (135.6 ± 5.5 µmoL/L) ($p < 0.05$)
Qi *et al.*, 2017[40]	Nephrotoxic drug-induced AKI/ Cisplatin administration	Serum urea	Lower levels in the groups that received 200 and 400 mg/kg of *P. ginseng* compared to CG ($p < 0.01$)
		Serum creatinine	Lower levels in the groups that received 200 and 400 mg/kg of *P. ginseng* compared to CG ($p < 0.01$)
Li *et al.*, 2019[45]	Nephrotoxic drug-induced AKI/ Cisplatin administration	Serum urea	Lower levels in the groups receiving 40 and 80 mg/kg of the arginyl-fructosyl-glucose compared to the CG ($p < 0.05$ and $p < 0.01$, respectively)
		Serum creatinine	Lower levels in the groups receiving 40 and 80 mg/kg of the arginyl-fructosyl-glucose compared to the CG ($p < 0.05$ and $p < 0.01$, respectively)

Author, year	Animal model of nephropathy/ Method of nephropathy induction	Biochemical markers for assessing renal function	Main outcomes
Wei *et al.*, 2021[52]	Nephrotoxic drug-induced AKI/ Cisplatin administration	Serum urea	Lower levels in the groups that received 200 and 400 mg/kg of the *P. ginseng* polysaccharides compared to the CG ($p < 0.001$ and $p < 0.01$, respectively)
		Serum creatinine	Lower levels in the groups that received 200 and 400 mg/kg of the *P. ginseng* polysaccharides compared to the CG ($p < 0.01$ and $p < 0.05$, respectively)
Li *et al.*, 2016[55]	Nephrotoxic drug-induced AKI/ Cisplatin administration	Serum urea	Lower levels in groups receiving 10 mg/kg (12.80 ± 1.36 mmol/L) and 20 mg/kg (11.70 ± 1.05 mmol/L) of the ginsenoside Rg5 compared to CG (14.20 ± 2.11 mmol/L) ($p < 0.05$ and $p < 0.01$, respectively)
		Serum creatinine	Lower levels in groups receiving 10 mg/kg (97.96 ± 3.12 µmol/L) and 20 mg/kg (45.00 ± 2.15 µmol/L) of the ginsenoside Rg5 compared to CG (201.34 ± 6.23 µmol/L) ($p < 0.05$ and $p < 0.01$, respectively)
Kim *et al.*, 2014[14]	Nephrotoxic drug-induced AKI/ Cisplatin administration	Serum urea	Lower levels in the groups receiving 100, 300 and 500 mg/kg of *P. ginseng* compared to CG ($p < 0.05$)
		Serum creatinine	Lower levels in the group receiving 100 mg/kg of *P. ginseng* compared to CG ($p < 0.05$)
Baek *et al.*, 2017[15]	Nephrotoxic drug-induced AKI/ Cisplatin administration	Serum urea	Lower levels in the groups receiving 2 mg/kg (38.63 ± 4.51 mg/dL) and 6 mg/kg of the ginsenosides Rk3 and Rh4 (33.60 ± 4.68 mg/dL) compared to the CG (47.07 ± 6.76 mg/dL) ($p < 0.05$ and $p < 0.01$, respectively)
		Serum creatinine	Lower levels in groups receiving 2 mg/kg (1.95 ± 0.36 mg/dL) and 6 mg/kg (1.80 ± 0.35 mg/dL) of the ginsenosides Rk3 and Rh4 compared to CG (2.67 ± 0.55 mg/dL) ($p < 0.05$ and $p < 0.01$, respectively)
Yokozawa *et al.*, 2000[33]	Nephrotoxic drug-induced AKI/ Cisplatin administration	Serum urea	Lower levels in the groups receiving 1 mg/kg (68.6 ± 3.5 mg/dL) and 5 mg/kg (60.8 ± 4.7 mg/dL) of the ginsenoside Rd compared to the CG (80.3 ± 7.3 mg/dL) ($p < 0.01$ and $p < 0.001$, respectively)
		Serum creatinine	Lower levels in the group receiving 5 mg/kg of the ginsenoside Rd (2.54 ± 0.26 mg/dL) compared to the CG (3.22 ± 0.26 mg/dL) ($p < 0.001$)
Jung *et al.*, 2017[34]	Nephrotoxic drug-induced AKI/ Cisplatin administration	Serum creatinine	There was no significant difference between the group receiving 150 mg/kg *P. ginseng* and the CG
		Creatinine clearance	Higher levels in the group that received 150 mg/kg of *P. ginseng* compared to CG ($p < 0.05$)
Park *et al.*, 2015[35]	Nephrotoxic drug-induced KI/ Cisplatin administration	Serum creatinine	Lower levels in the group in the group that received 25 mg/kg of the heat-processed, methanol-extracted extract of *P. ginseng* compared to the CG ($p < 0.05$). There was no significant difference in the groups receiving 100 mg/kg of the white ginseng extract and heat-processed extract of *P. ginseng*
Zhang *et al.*, 2021[46]	Nephrotoxic drug-induced KI/ Cisplatin administration	Serum urea	Lower levels in the groups that received 10 and 20 mg/kg of the ginsenoside 20(R)Rg3 compared to the CG ($p < 0.05$ and $p < 0.01$, respectively)
		Serum creatinine	Lower levels in groups receiving 10 and 20 mg/kg of the ginsenoside 20(R)Rg3 compared with CG ($p < 0.01$)
Qi *et al.*, 2019[47]	Nephrotoxic drug-induced KI/ Cisplatin administration	Serum urea	Lower levels in the groups that received 20 and 40 mg/kg of the ginsenoside Rh2 and 40 mg/kg of the dihydroginsenoside 2H-Rh2 from *P. ginseng* compared to the CG ($p < 0.01$)
		Serum creatinine	Lower levels in the groups that received 20 and 40 mg/kg of the ginsenoside Rh2 ($p < 0.01$) and 40 mg/kg of the dihydroginsenoside 2H-Rh2 ($p < 0.05$) from *P. ginseng* compared to the CG
Zhai *et al.*, 2021[36]	Nephrotoxic drug-induced KI/ Cisplatin administration	Serum urea	Lower levels in the group receiving 5 mg/kg of the ginsenoside Rg3 compared to the CG ($p < 0.001$)
		Serum creatinine	Lower levels in the group receiving 5 mg/kg of the ginsenoside Rg3 compared to the CG ($p < 0.001$)

Author, year	Animal model of nephropathy/ Method of nephropathy induction	Biochemical markers for assessing renal function	Main outcomes
Yousef *et al.*, 2015[16]	Nephrotoxic drug-induced AKI/ Cisplatin administration	Serum urea	Lower levels in the group receiving 100 mg/kg (61.65 ± 1.92 mg/dL) of *P. ginseng* compared to the CG (85.80 ± 2.59 mg/dL) ($p < 0.05$)
		Serum creatinine	Lower levels in the group receiving 100 mg/kg (1.53 ± 0.093 mg/dL) of *P. ginseng* compared to CG (2.63 ± 0.104 mg/dL) ($p < 0.05$)
Kalkan *et al.*, 2012[17]	Nephrotoxic drug-induced AKI/ Gentamicin administration	Serum urea	Lower levels in the group receiving 100 mg/kg (72.38 ± 5.75 mg/dL) and 200 mg/kg (40.80 ± 7.50 mg/dL) of *P. ginseng* compared to the CG (96.25 ± 9.50 mg/dL) ($p < 0.05$)
		Serum creatinine	Lower levels in the group receiving 100 mg/kg (0.95 ± 0.15 mg/dL) and 200 mg/kg (0.45 ± 0.20 mg/dL) of *P. ginseng* compared to the CG (1.55 ± 0.25 mg/dL) ($p < 0.05$)
Lee *et al.*, 2013[18]	Nephrotoxic drug-induced AKI/ Gentamicin administration	Serum urea	Lower levels in the group receiving 100 mg/kg (9.85 ± 6.07 mg/dL) of *P. ginseng* compared to CG (176 ± 78.1 mg/dL) ($p < 0.05$)
		Creatinine *clearance*	Higher levels in the group receiving 100 mg/kg (3.18 ± 1.10 mL/min/kg) of *P. ginseng* compared to CG (0.0837 ± 0.0451 mL/min/kg) ($p < 0.05$)
Shin *et al.*, 2014[19]	Nephrotoxic drug-induced AKI/ Gentamicin administration	Serum urea	Lower levels in the group receiving 100 mg/kg of *P. ginseng* compared to CG ($p < 0.05$) after 10 days of treatment
		Serum creatinine	Lower levels in the group receiving 100 mg/kg of *P. ginseng* compared to CG ($p < 0.05$) after 10 days of treatment
		Proteinuria	Lower levels in the group receiving 100 mg/kg *P. ginseng* compared to CG ($p < 0.05$) after 3 and 10 days of treatment
Qadir *et al.*, 2011[37]	Nephrotoxic drug-induced KI/ Gentamicin administration	Serum urea	Lower levels in the group receiving 100 mg/kg (47.73 ± 0.69 mg/dL) of *P. ginseng* compared to the CG (66.40 ± 0.54 mg/dL) ($p<0.001$)
		Serum creatinine	Lower levels in the group receiving 100 mg/kg (0.68 ± 0.08 mg/dL) of *P. ginseng* compared to the CG (1.41 ± 0.08 mg/dL) ($p<0.001$)
Karadeniz *et al.*, 2008[20]	Nephrotoxic drug-induced AKI/ Gentamicin administration	Serum urea	Lower levels in the group receiving 200 mg/kg of *P. ginseng* (0.70 ± 0.06 g/L) compared to CG (1.05 ± 0.07 g/L) ($p < 0.05$)
		Serum creatinine	Lower levels in the group receiving 200 mg/kg of *P. ginseng* (8.9 ± 1.3 g/L) compared to CG (14.2 ± 2.1 g/L) ($p < 0.05$)
Lim *et al.*, 2014[41]	Nephrotoxic drug-induced CKI/ Ciclosporin administration	Serum creatinine	Lower levels in the groups that received 200 and 400 mg/kg of *P. ginseng* compared to CG ($p < 0.05$)
		Albuminuria	There was no significant difference between the groups that received 200 and 400 mg/kg of *P. ginseng* and the CG
Doh *et al.*, 2013[38]	Nephrotoxic drug-induced CKI/ Ciclosporin administration	Serum urea	Lower levels in the group receiving 400 mg/kg (15.3 ± 1.4 mg/dL) of *P. ginseng* compared to CG (19.7 ± 1.6 mg/dL) ($p < 0.05$)
		Serum creatinine	There was no significant difference between the groups that received 200 and 400 mg/kg of *P. ginseng* and the CG
		Creatinine *clearance*	Higher levels in the groups receiving 200 mg/kg (0.24 ± 0.06 mL/min/100 g) and 400 mg/kg (0.20 ± 0.05 mL/min/100 g) of *P. ginseng* compared to CG (0.08 ± 0.02 mL/min/100 g) ($p < 0.05$)
Fan *et al.*, 2016[48]	Nephrotoxic drug-induced KI/ d-galactose administration	Serum urea	Lower levels in the group receiving 20 mg/kg (15.77 ± 1.22 mmol/L) of the ginsenoside Rg1 compared to the CG (17.19 ± 1.09 mmol/L) ($p < 0.05$)
		Serum creatinine	Lower levels in the group receiving 20 mg/kg (22.60 ± 3.97 µmol/L) of the ginsenoside Rg1 compared to the CG (29.40 ± 5.72 µmol/L) ($p < 0.05$)
Li *et al.*, 2020[49]	Nephrotoxic drug-induced KI/ d-galactose administration	Serum urea	Lower levels in groups receiving 10 mg/kg and 20 mg/kg of the ginsenoside 20(R)Rg3 compared with CG ($p < 0.01$)
Sun *et al.*, 2013[50]	Ischemia-induced AKI/ Mesenteric Artery Occlusion	Serum urea	Lower levels in the group receiving 6 mg/mL of the ginsenoside Rb1 compared to CG ($p < 0.05$)
		Serum creatinine	Lower levels in the group receiving 6 mg/mL of the ginsenoside Rb1 compared to CG ($p < 0.05$)

Author, year	Animal model of nephropathy/ Method of nephropathy induction	Biochemical markers for assessing renal function	Main outcomes
Kim *et al*., 2013[21]	Drug-induced CKI/ Adenine administration	Serum urea	Lower levels in the groups receiving 100 mg/kg of the aqueous extract (78.0 ± 2.71 mg/dL on day 10 and 128.9 ± 8.59 mg/dL on day 20, $p < 0.05$), the 25 mg/kg of the extract with butanol (75.2 ± 3.48 mg/dL on day 10 and 126.8 ± 4.65 mg/dL on day 20, $p < 0.05$) and 50 mg/kg of the extract with butanol (69.1 ± 5.83 mg/dL on day 10 and 118.2 ± 9.20 mg/dL on day 20, $p < 0.01$) from *P. ginseng* compared to GC (91.5 ± 6.19 mg/dL on day 10) (150.2 ± 6.73 mg/dL on day 20) ($p < 0.05$)
		Serum creatinine	Lower levels in the groups receiving 100 mg/kg of the aqueous extract (0.98 ± 0.07 mg/dL on day 10 and 1.81 ± 0.10 mg/dL on day 20, $p < 0.05$) and 50 mg/kg of the butanol-containing extract (0, 93 ± 0.07 mg/dL on day 10, $p < 0.01$, and 1.76 ± 0.12 mg/dL on day 20, $p < 0.05$) of *P. ginseng* compared to GC (1.14 ± 0.06 mg/dL on day 10 and 2.14 ± 0.13 mg/dL on day 20)
Ragab *et al*., 2021[39]	Nephrotoxic drug--induced KI/Nitroarginine administration	Serum urea	Lower levels in groups that received 100 mg/kg *P. ginseng* compared to CG ($p < 0.01$)
		Serum creatinine	Lower levels in groups that received 100 mg/kg *P. ginseng* compared to CG ($p < 0.01$)
Elblehi *et al*., 2019[42]	Nephrotoxic drug--induced KI/ Hydroxyurea administration	Serum urea	Lower levels in the group receiving 200 mg/kg (53.84 ± 4.00 mg/dL) of *P. ginseng* compared to CG (80.40 ± 2.94 mg/dL) ($p < 0.05$)
		Serum creatinine	Lower levels in the group receiving 200 mg/kg (0.63 ± 0.01 mg/dL) of *P. ginseng* compared to CG (0.76 ± 0.01mg/dL) ($p < 0.05$)
El *et al*., 2016[53]	Nephrotoxic drug-induced KI/ Litium administration	Serum urea	Lower levels in the group receiving 100 mg/kg (5.5 ± 0.8 mg/dL) of the ginsenoside Rb1 compared to the CG (9.1 ± 2.1 mg/dL) ($p < 0.05$)
		Serum creatinine	Lower levels in the group receiving 100 mg/kg (0.91 ± 0.09 mg/dL) of the ginsenoside Rb1 compared to the CG (4.23 ± 0.57 mg/dL) ($p < 0.05$)
		Creatinine clearance	Higher levels in the group receiving 100 mg/kg (0.37 ± 0.01 mL/min) of the ginsenoside Rb1 compared to the CG (0.03 ± 0.01 mL/min) ($p < 0.05$)
		Albuminuria	Lower levels in the group receiving 100 mg/kg (1.36 ± 0.14 mg/dL) of the Rb1 ginsenoside compared to GC (2.65 ± 0.25 mg/dL) ($p < 0.05$) and the urinary albumin/creatinine ratio was lower in the group receiving 100 mg/kg (32 ± 7 mg/g) of the Rb1 ginsenoside compared to GC (96 ± 6 mg/g) ($p < 0.05$)
El *et al*., 2012[22]	Nephrotoxic substance--induced KI/ Administration of carbon tetrachloride	Serum urea	Lower levels in the group that received 20 mg/kg (77.57 ± 2.66 mg/dL) of *P. ginseng* compared to the CG (142.04 ± 4.32 mg/dL) ($p \leq 0.05$)
		Serum creatinine	Lower levels in the group receiving 20 mg/kg (2.85 ± 0.12 mg/dL) of *P. ginseng* compared to the CG (3.37 ± 0.43 mg/dL) ($p \leq 0.05$)
Mansour, 2013[43]	Gamma radiation induced KI / Gamma radiation exposure	Serum urea	Lower levels in the group receiving 100 mg/kg (54.8 ± 2.1 mg/dL) of *P. ginseng* compared to CG (65.4 ± 3.0 mg/dL) ($p < 0.05$)
		Serum creatinine	Lower levels in the group receiving 100 mg/kg (1.32 ± 0.07 mg/dL) of *P. ginseng* compared to CG (3.01 ± 0.09 mg/dL) ($p < 0.05$)

DKD= diabetes kidney disease; DM= Diabetes Mellitus; T2DM= type 2 diabetes mellitus; AKI= acute kidney injury; CKI= chronic kidney injury; KI= kidney injury; CG= control group.

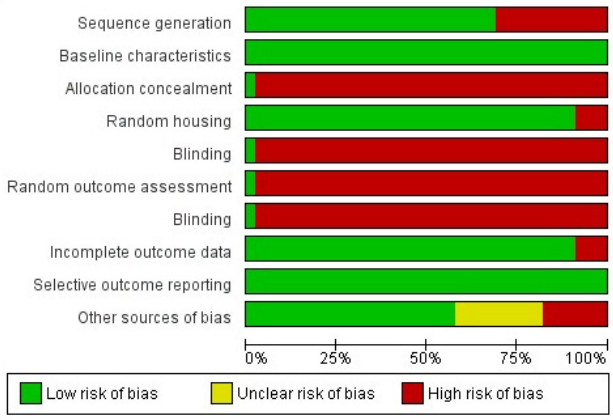

Figure 2. Risk of bias assessment according to SYRCLE tool10.

Other sources of bias were defined as the presence of conflict of interest among the authors.

DISCUSSION

Most of the pre-clinical studies included in this systematic review demonstrated that *P. ginseng* has a nephroprotective effect in different animal models of nephropathy, promoting significant improvements in biochemical parameters for the evaluation of renal function: serum creatinine, serum urea, creatinine clearance, proteinuria and albuminuria.

DKD is a major cause of end-stage renal disease, and a significant proportion of individuals with type 1 (T1DM) and type 2 diabetes mellitus (T2DM) are affected worldwide.[56]

Among the 16 studies that evaluated the nephroprotective effect of *P. ginseng* in DKD, 11 observed improvements in all the biochemical parameters of renal function evaluation analyzed, three verified improvements in part of the biochemical markers analyzed and only two did not verify improvement in any of the markers.

The nephroprotective effect of *P. ginseng* in DKD can be explained by its hypoglycemic effect, which results in decreased formation of advanced glycation end products (AGEs).[25] AGEs can damage cells through changes in their intracellular structures, interaction with extracellular matrix proteins, modifying signaling and causing dysfunction, and also by promoting modifications in proteins or blood lipids, which can bind to receptors and promote the production of inflammatory cytokines and growth factors, responsible for the development of vascular complications of DM such as DKD.[57]

The decrease in glucose through the use of *P. ginseng* can also be explained by decreased intestinal absorption of glucose and/or increased glucose disposal and insulin secretion,[30] thus preventing complications such as DKD. A double-blind randomized controlled clinical trial further demonstrated that the administration of *P. ginseng* in patients with T2DM reduced fasting blood glucose levels and insulin resistance, demonstrating this hypoglycemic effect of *P. ginseng*, which may contribute to the prevention and mitigation of DKD.[58]

In addition, *P. ginseng* can suppress inflammatory pathways, with decreased plasma levels of tumor necrosis factor alfa (TNF-α),[28] in addition to the expression of the thioredoxin interaction protein (*TXNIP*) gene, which is activated under high glucose concentrations and participates in the oxidative stress process and is involved in the inflammatory process by activating the NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome, which promotes an increased inflammatory response[23].

The overexpression of NLRP3, apoptosis-associated speck-like protein containing a CARD (ASC), caspase-1, interleukin 1 (IL-1) and interleukin 18 (IL-18) proteins in the kidneys was suppressed with the use of ginsenosides. In addition, a decrease in TXNIP levels was also found, demonstrating that ginsenosides can inhibit the secretion of inflammatory cytokines and TXNIP-mediated activation of the NLRP3 inflammasome, protecting the kidneys.[23]

Renal fibrosis can be induced by peritubular cell proliferation and collagen deposition stimulated by transforming growth factor beta (TGF-β). The accumulation of extracellular matrix in the kidneys is the main cause of fibrosis, which may lead to renal dysfunction.[12] *P. ginseng* is effective in reducing the expression of TGF-β, AGEs and kidney injury molecule 1 (KIM1), and is an important ally in renal protection.[12] The attenuation of the renal fibrosis process can also be explained by inhibition of the activation of the cAMP/PKA/CREB (cyclic adenosine 3', 5 monophosphate/ protein kinase A/ response element binding protein) signaling pathway.[24]

P. ginseng also promotes a reduction in oxidative stress by inhibiting lipid peroxidation[29] and eliminating free radicals[32]. It possesses antifibrotic and pro-autophagic effects by reversing the epithelial-mesenchymal transition of podocytes and increasing autophagy mediated by the AKT/GSK3β/β-catenin (protein kinase B/ glycogen synthase kinase beta/ beta catenin) pathway.[13] The production of reactive oxygen species (ROS) in DKD is mainly related to the activation of NAD(P)H oxidase (NOX4), which results in decreased antioxidant capacity of cells. Excessive amounts of ROS promote activation of mitogen-activated protein kinase C (MAPK) and activation of transcription factors and inflammatory cytokines, which may lead to end-stage renal disease.[23] *P. ginseng* is effective in reducing NAD(P)H oxidase expression, and consequently, in decreasing oxidative stress in the kidneys.[23]

Systemic arterial hypertension is another important underlying disease of CKD and a major cause of end-stage renal disease, and the prevention and treatment of kidney disease secondary to hypertension is a challenge.[59] Nitroarginine is capable of inducing hypertension, increased levels of oxidative stress markers, and depletion of nitric oxide (NO) activity and biosynthesis, which leads to vasoconstriction, and consequently, renal failure.[39]

One of the studies included in this systematic review found that *P. ginseng* extract reduced serum urea and creatinine levels in animals with nitroarginine-induced nephropathy by raising malondialdehyde (MDA) and NO levels and reducing TNF-α.[39] Therefore, the use of *P. ginseng* is promising in preventing or delaying renal failure secondary to hypertension.

It is also noteworthy that several widely marketed and useful drugs today are potentially nephrotoxic, such as cisplatin, gentamicin, and cyclosporine. Therefore, the use of phytotherapeutics with potential nephroprotective effects, such as *P. ginseng* is promising in alleviating the nephrotoxic effect.[4]

A potent anticancer drug used in clinical practice is cisplatin, which presents its nephrotoxic effect as a limiting factor for its use. The mechanisms involving its nephrotoxicity are multifactorial and complex, among them, we can mention preferential accumulation in proximal tubular cells, metabolic activation, oxidative injury, cell death, inflammatory tissue injury, and renal failure.[15] Among the thirteen studies that evaluated the nephroprotective effect of *P. ginseng* on cisplatin-induced nephropathy, all showed improvement in the biochemical parameters of renal function evaluation analyzed, except for one study[34] which did not see a reduction in creatinine levels, but did see an increase in creatinine clearance.

Oxidative injury is considered an early effect of cisplatin toxicity and is characterized by glutathione (GSH) depletion and the presence of reactive cisplatin binding thiol conjugates, which trigger a cellular imbalance, and consequently, oxidative stress and kidney tissue loss. Ginsenosides showed a great potential to recover the activity of antioxidant enzymes in the kidney, such as superoxide dismutase (SOD) and catalase (CAT), which are key in the metabolism of ROS and recycling of GSH, reducing oxidative injury.[15] In addition, ginsenosides were effective in reducing the concentration of MDA, an oxidizing enzyme that contributes to the development of kidney damage,[14] and decreased the expression of 4-Hydroxynonenal (4--HNE), another marker of oxidative damage.[40]

Still, the increase of inflammatory cytokines such as TNF-α, IL-1, inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) is observed in cisplatin-induced nephrotoxicity, but suppression of TNF-α and IL-1 and significant decrease of iNOS and COX-2 expression was observed with the use of *P. ginseng.*[40] Tubular necrosis is one of the main characteristics of acute renal failure caused by cisplatin, the use of *P. ginseng* decreased the severity of necrosis and also provided improvements such as milder desquamation and decreased atrophy of tubular epithelial cell.[14] Therefore, the use of *P. ginseng* in the prevention of cisplatin-induced kidney damage is interesting due to its anti-inflammatory, antioxidant, and anti-fibrotic properties, among others.

Hydroxyurea is another drug used in the treatment of tumors that is potentially nephrotoxic. This drug is capable of inducing the generation of ROS, due to the production of intermediates of its metabolism, such as carbamoyl nitrones, which are transformed into nitroxide compounds that generate oxidative stress.[42] One of the studies included in this systematic review[42] reported that *P. ginseng*, by presenting an antioxidant effect, can decrease the renal lesions induced by hydroxyurea, reducing serum creatinine and urea levels.

Gentamicin is an antimicrobial widely used to treat infections caused by gram-negative bacteria, however, it has a significant nephrotoxic potential. This nephrotoxicity is due to the accumulation of the drug in tubular cells, resulting in oxidative stress, inflammation, and decreased glomerular filtration rate.[18]

All five studies included in this systematic review that evaluated the nephroprotective effect of *P. ginseng* on gentamicin-induced nephropathy found improvement in renal function assessment markers.

P. ginseng extract was shown to be effective in preventing kidney injury by reducing gentamicin accumulation in the renal tubule.[18] It is known that the use of this drug is often associated with combined therapy with metformin, an antidiabetic drug, even though it has a nephrotoxic character. However, pharmacokinetic studies of metformin have shown that the extract, in addition to providing prevention of kidney damage, also helps not to cause gentamicin-induced pharmacokinetic changes in the antidiabetic drug.[18]

Due to the formation of the drug-iron complex, gentamicin acts as an iron chelator, consisting of a potent catalyst of free radical formation.[20] *P. ginseng* has phenolic acids and flavonoids that increase renal blood flow and scavenge free radicals, preventing oxidative damage from gentamicin use.[37] This antioxidant effect also promotes the protection of renal tubular cells against apoptosis.[19]

Cyclosporine is an immunosuppressive drug widely used in clinical practice, however, chronic nephropathy caused by this drug is the leading cause of chronic graft dysfunction and graft failure in renal transplant recipients.[41] Cyclosporine causes excessive formation of autophagosomes and protein aggregates. The use of *P. ginseng* extract can promote an attenuation of excessive autophagic induction, besides promoting a decrease in interstitial inflammation, fibrosis and apoptotic cell death, presenting great potential in preventing cyclosporine-induced kidney injury.[38,41]

One of the studies included in this systematic review[41] demonstrated reduced serum creatinine levels, but not albuminuria, and the other[38] found reduced serum urea levels, but not creatinine, and increased creatinine clearance in animals with cyclosporine-induced nephropathy receiving *P. ginseng*.

D-galactose is used in the induction of nephropathy in animals, because it promotes the accumulation of ROS and the formation of AGEs by stimulating the production of free radicals, thus simulating normal aging.[48] The studies

included in this systematic review found that ginsenosides Rg1[48] and 20(R)Rg3[49] reduced biochemical markers for assessing kidney function by reducing oxidative stress, demonstrating its potential use for preventing age-related kidney damage.[48]

The antioxidant capacity of *P. ginseng* was also important for reversing structural and functional kidney cell damage, reducing biochemical markers for assessing renal function, in nephropathy caused by lithium,[53] carbon tetrachloride,[22] adenin,[21] exposure to gamma radiation[43] and caused by intestinal ischemia-reperfusion, which causes significant oxidative damage to the renal parenchyma and consequent loss of organ function.[50] Rb1 ginsenoside promoted a decrease in interstitial fibrosis, attenuated renal apoptosis and oxidative injury by activating the Nrf2/ARE (NF-E2-related factor 2/ antioxidant response element) pathway, which is responsible for minimizing this damage caused by intestinal ischemia-reperfusion.[50]

During the search for articles, only one clinical study was found that evaluated the nephroprotective effect of *P. ginseng* in humans.[8] This study used the ginsenoside Rb1 component of *P. ginseng* extracted from its root. The dose administered to patients with stage 2 and 3 CKD was 500 mg orally for six months. The sample size of the control and intervention groups was 86 and 91 patients, respectively.

Serum creatinine and urea levels significantly reduced while creatinine clearance significantly increased in the group receiving 500 mg/day of *P. ginseng* after 6 months of treatment ($p<0.01$) and these beneficial effects on renal function assessment markers remained for 6 months ($p<0.05$) after the end of treatment, while there was no significant difference in serum creatinine and urea levels and creatinine clearance in the group receiving placebo after 6 months of treatment. This result demonstrates that the nephroprotective effect of *P. ginseng* is also observed in humans, emphasizing its great therapeutic potential in DKD.

A clinical study evaluated the safety and tolerability of 500 mg and 1000 mg of *P. ginseng* extract administered twice daily in 170 healthy volunteers for 4 weeks and found only mild adverse events occurred, such as insomnia, gastrointestinal disorders (dyspepsia, abdominal pain, nausea, diarrhea, and constipation), headaches, dizziness, insomnia, heat waves, and skin changes. The administration of *P. ginseng* did not significantly alter the levels of biochemical and hematological parameters.[60]

Some clinical trials in which patients with chronic obstructive pulmonary disease received treatment with 100 mg of *P. ginseng* extract twice a day for twelve months still found it to be safe and well tolerated even with long-term treatment.[61,62] Furthermore, the clinical trial evaluating the nephroprotective effect of *P. ginseng* in patients with CKD did not observe any adverse effects related to *P. ginseng* supplementation, ratifying the safety and efficacy of *P. ginseng* for this purpose.[7]

A limitation of this systematic review is the large variation among studies regarding doses administered, routes of administration, duration of treatment, and size of control and intervention groups, which may explain the divergence of results observed in a few studies and made it impossible to carry out a meta-analysis. In the risk of bias assessment, a high risk of bias was observed for some questions, main regarding selection, performance and detection bias, which is another limitation. However, it is important to emphasize that the high risk of bias in some questions does not devalue the results, since blinding is not common in pre-clinical trials.

Despite these small limitations, many studies were included in this systematic review and most found that *P. ginseng* has a nephroprotective action in different animal models of nephropathy. Therefore, it is very important to carry out more clinical trials to prove this beneficial effect in humans so that *P. ginseng* can be widely used in clinical practice as a nephroprotective herbal medicine.

CONCLUSION

P. ginseng derivatives display significant nephroprotective effects in different animal models of nephropathy. Therefore, its use is promising as an adjuvant in the treatment of DKD and in the prevention of drug-induced nephropathy. It is noteworthy that given such promising results in preclinical studies, controlled-randomized clinical trials would be strongly recommended for the consolidation of this phytopharmaceutical as a nephroprotective drug.

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Contributorship Statement

PTCO: Conception and design, acquisition of data, analysis and interpretation of data, drafting the article.
ROC, NRB, AO: Analysis and interpretation of data, revising it critically for important intellectual content.
CPD: Conception and design, acquisition of data, analysis and interpretation of data, drafting the article. revising it critically for important intellectual contente, final approval of the version to be published.

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Supplementary Material

The Medical Subject Headings (MeSH) was used to define these descriptors and the selection of articles was made using the following search strategy:
("Renal Insufficiency, Chronic" OR "Chronic Renal Insufficiencies" OR "Renal Insufficiencies, Chronic" or "Chronic Renal Insufficiency" or "Kidney Insufficiency, Chronic" or "Chronic Kidney Insufficiency" or "Chronic Kidney Insufficiencies" or "Kidney Insufficiencies, Chronic" or "Chronic Kidney Diseases" or "Chronic Kidney Disease" or "Disease, Chronic Kidney" or "Diseases, Chronic Kidney" or "Kidney Disease, Chronic" or "Kidney Diseases, Chronic" or "Chronic Renal Diseases" or "Chronic Renal Disease" or "Disease, Chronic Renal" or "Diseases, Chronic Renal" or "Renal Disease, Chronic" or "Renal Diseases, Chronic" or "Diabetic Nephropathies" or "Nephropathies, Diabetic" or "Nephropathy, Diabetic" or "Diabetic Nephropathy" or "Diabetic Kidney Disease" or "Diabetic Kidney Diseases" or "Kidney Disease, Diabetic" or "Kidney Diseases, Diabetic" or "Diabetic Glomerulosclerosis" or "Glomerulosclerosis, Diabetic" or "Intracapillary Glomerulosclerosis" or "Nodular Glomerulosclerosis" or "Glomerulosclerosis, Nodular" or "Kimmelstiel-Wilson Syndrome" or "Kimmelstiel Wilson Syndrome" or "Syndrome, Kimmelstiel-Wilson" or "Kimmelstiel-Wilson Disease" or "Kimmelstiel Wilson Disease" or "Hypertensive Nephropathy" or "Hypertension, Renal" or "Nephritis" or "Acute Kidney Injury" or "Acute Kidney Injuries" or "Kidney Injuries, Acute" or "Kidney Injury, Acute" or "Acute Renal Injury" or "Acute Renal Injuries" or "Renal Injuries, Acute" or "Renal Injury, Acute" or "Renal Insufficiency, Acute" or "Acute Renal Insufficiencies" or "Renal Insufficiencies, Acute" or "Acute Renal Insufficiency" or "Kidney Insufficiency, Acute" or "Acute Kidney Insufficiencies" or "Kidney Insufficiencies, Acute" or "Acute Kidney Insufficiency" or "Kidney Failure, Acute" or "Acute Kidney Failures" or "Kidney Failures, Acute" or "Acute Renal Failure" or "Acute Renal Failures" or "Renal Failures, Acute" or "Renal Failure, Acute" or "Acute Kidney Failure" or "Nephrotoxicity") and ("Panax" or "Ninjin" or "Ninjins" or "Renshen" or "Renshens" or "Shinseng" or "Shinsengs" or "Jen Shen" or "Jen Shens" or "Shen, Jen" or "Ginseng" or "Ginsengs" or "Schinseng" or "Schinsengs" or "Korean Red Ginseng" or "Ginseng, Korean Red" or "Korean Red Ginsengs" or "Red Ginseng, Korean" or "Korean Ginseng" or "Ginseng, Korean" or "Korean Ginsengs" or "Panax ginseng").