REVIEW ARTICLE

Nephroprotective effect of *panax notoginseng*

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ABSTRACT

Objective: This systematic review aimed to evaluate the nephroprotective effect of *Panax notoginseng*. **Methods:** The search for scientific articles in the literature was carried out in the Medline (PubMed), Web of Science, Embase, and Virtual Health Library (BVS) databases. Eligibility criteria consisted of preclinical *in vivo* or clinical studies that demonstrated the nephroprotective effect of *Panax notoginseng*, as assessed by one or more of the following laboratory tests: serum creatinine, serum urea, glomerular filtration rate, creatinine clearance, proteinuria, or albuminuria. **Results:** Fourteen articles were included, all of which consisted of preclinical trials. The nephropathy models used in the studies were diabetic kidney disease (n=8), kidney injury induced by nephrotoxic substances (n=5), or ischemia (n=1). All studies showed that *Panax notoginseng* has a nephroprotective effect when used in the treatment of kidney diseases. Although three studies did not observe a reduction in serum creatinine and/or urea levels, these studies found that albuminuria decreased significantly. **Conclusion:** *Panax notoginseng* has a nephroprotective effect in different animal models of nephropathy. The clinical use of *Panax notoginseng* tends to be promising as an adjuvant in the pharmacotherapy of renal dysfunctions and in the prevention of drug-induced nephrotoxicity.

Keywords: Acute kidney injury, Diabetic nephropathies, Chronic renal insufficiency, *Panax notoginseng*.

INTRODUCTION

Panax notoginseng is a species belonging to the genus *Panax* and the Araliaceae family. It consists of an erect perennial herb, which can reach heights of up to 60 cm. Known in China as Sanqi or Tianqi, it is a medicinal plant valued and widely used in Asia. Increasing pharmacological and clinical evidence indicates that *Panax notoginseng* has multiple beneficial effects, which are mainly due to the saponins present in its composition. Saponins are one of the main active components of the *Panax notoginseng* and *Panax ginseng* species, with the saponin content present in *Panax notoginseng* being approximately three times higher than that of *Panax ginseng*. Among the other active chemical constituents are polysaccharides, dencichin, flavonoids, fatty acids, and volatile oil, which are found in its dried root, the main part used for medicinal purposes.

Panax notoginseng has a wide range of pharmacological effects described by scientific studies, including anti-cancer, neuroprotective, and anti-inflammatory actions. It is also used as an immunological adjuvant and in the prevention of diabetes mellitus complications. The International Diabetes Federation estimated that 537 million people were living with diabetes in 2021, and it is projected that around 40% or more of these individuals will develop diabetic kidney disease, one of the complications of diabetes mellitus. This condition is the leading cause of entry into renal replacement therapy and is associated with increased morbidity and mortality. There is

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evidence that *Panax notoginseng* has the ability to delay the progression of renal fibrosis, improve hemorheology and renal microcirculation, significantly reducing urinary protein excretion in patients with diabetic kidney disease, thus preventing kidney damage.

Drugs that inhibit the renin-angiotensin system (RAS), such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), have a nephroprotective action and are currently used in the treatment of chronic kidney disease (CKD), reducing the risk of disease progression. The use of *Panax notoginseng* as a nephroprotective agent in the adjuvant treatment of CKD has been evaluated and shows promise.

The promising nephroprotective effect of *Panax notoginseng* can also be discussed in the context of attenuating the nephrotoxicity of some drugs. It is well known that the use of medications is a relatively common cause of acute and chronic kidney injury. However, the use of these drugs is essential for treating various diseases, given the indispensability of their therapeutic effects. Examples of medications with nephrotoxic potential include antimicrobials, antitumor agents, analgesics, and immunosuppressants. Studies have reported the nephroprotective effect of *Panax notoginseng* in mice treated with nephrotoxic drugs such as cisplatin, adriamycin, and polymyxin E. In these animals, *Panax notoginseng* was able to improve renal function, inhibit oxidative stress, and prevent apoptosis in renal tissue.

This systematic review aims to elucidate the nephroprotective effect of *Panax notoginseng*, validating its wide range of pharmacological effects, which could be significant in defining clinical practice procedures.

METHODOLOGY

Search strategy

The Medline (PubMed), Web of Science, Embase and Virtual Health Library (VHL) databases were used to search for scientific articles in the literature. The selection was carried out using the descriptors defined by Medical Subject Headings (MeSH) “Renal Insufficiency, Chronic”; “Chronic Renal Insufficiencies”; “Renal Insufficiencies, Chronic”; “Chronic Renal Insufficiency” or “Kidney Insufficiency, Chronic” or “Chronic Kidney Insufficiency”; “Chronic Kidney Insufficiencies”; “Kidney Insufficiencies, Chronic”; “Chronic Kidney Diseases”; “Chronic Kidney Disease”; “Disease, Chronic Kidney”; “Diseases, Chronic Kidney”; “Kidney Disease, Chronic”; “Kidney Diseases, Chronic”; “Chronic Renal Diseases”; “Chronic Renal Disease”; “Disease, Chronic Renal”; “Diseases, Chronic Renal”; “Renal Disease, Chronic”; “Renal Diseases, Chronic”; “Diabetic Nephropathies”; “Nephropathies, Diabetic”; “Nephropathy, Diabetic”; “Diabetic Nephropathy”; “Diabetic Kidney Disease”; “Diabetic Kidney Diseases”; “Kidney Disease, Diabetic”; “Kidney Diseases, Diabetic”; “Diabetic Glomerulosclerosis”; “Glomerulosclerosis, Diabetic”; “Intracapillary Glomerulosclerosis”; “Nodular Glomerulosclerosis”; “Glomerulosclerosis, Nodular”; “Kimmelstiel-Wilson Syndrome”; “Kimmelstiel Wilson Syndrome”; “Syndrome, Kimmelstiel-Wilson”; “Kimmelstiel-Wilson Disease”; “Kimmelstiel Wilson Disease”; “Hypertensive Nephropathy”; “Hypertension, Renal”; “Nephritis”; “Acute Kidney Injury”; “Acute Kidney Injuries”; “Kidney Injuries, Acute”; “Kidney Inju-

ry, Acute"; "Acute Renal Injury"; "Acute Renal Injuries"; "Renal Injuries, Acute"; "Renal Injury, Acute"; "Renal Insufficiency, Acute"; "Acute Renal Insufficiencies"; "Renal Insufficiencies, Acute"; "Acute Renal Insufficiency"; "Kidney Insufficiency, Acute"; "Acute Kidney Insufficiencies"; "Kidney Insufficiencies, Acute"; "Acute Kidney Insufficiency"; "Kidney Failure, Acute"; "Acute Kidney Failures"; "Kidney Failures, Acute"; "Acute Renal Failure"; "Acute Renal Failures"; "Renal Failures, Acute"; "Renal Failure, Acute"; "Acute Kidney Failure"; "Nephrotoxicity" in combination with the descriptors "Panax"; "Ninjin"; "Ninjins"; "Renshen"; "Renshens"; "Shinseng"; "Shinsengs"; "Jen Shen" or "Jen Shens"; "Shen, Jen"; "Ginseng"; "Ginsengs"; "Schinseng"; "Schinsengs"; "Korean Red Ginseng"; "Ginseng, Korean Red"; "Korean Red Ginsengs"; "Red Ginseng, Korean"; "Korean Ginseng"; "Ginseng, Korean"; "Korean Ginsengs"; "Panax ginseng"; "Panax notoginseng"; "Panax notoginsengs"; "notoginsengs, Panax", using the "AND" connector between the terms.

Eligibility criteria

The eligibility criteria were established in accordance with the PRISMA recommendation (2020)[10], and consisted of *in vivo* clinical or pre-clinical trials, which evaluate the nephroprotective effect of *Panax notoginseng*. Only articles whose experimental design met the following criteria, according to the PICOS acronym, were included in the systematic review:

Population: patients or animals with chronic kidney disease, diabetic kidney disease, hypertensive nephropathy, acute kidney injury, or kidney injury induced by medications or other nephrotoxic agents that received *Panax notoginseng*.

Intervention: administration of *Panax notoginseng*.

Control: patients or animals with chronic kidney disease, diabetic kidney disease, hypertensive nephropathy, acute kidney injury, or kidney injury induced by medications or other nephrotoxic agents that did not receive *Panax notoginseng*.

Outcome: nephroprotective effect assessed through one or more of the following laboratory tests: serum creatinine, serum urea, glomerular filtration rate, creatinine clearance, proteinuria, albuminuria.

Study design: *in vivo* preclinical trial or clinical trial.

There was no restriction on the date of publication or language of the articles. Studies that evaluated the use of ***Panax notoginseng*** in combination with another substance and those that did not utilize the biochemical markers serum creatinine, serum urea, glomerular filtration rate, creatinine clearance, proteinuria, or albuminuria were excluded from the systematic review. ***In vitro*** assays were also excluded. The database search for articles was conducted up until May 27, 2022. The authors of unavailable articles were contacted twice via email to request access to these articles; however, no responses were received.

Selection of Articles

The articles were selected in two stages, both conducted independently by two reviewers. In the first stage, duplicate articles were excluded, and the titles and abstracts were reviewed to include only *in vivo* clinical or pre-clinical trials that as-

sessed the nephroprotective effect of *Panax notoginseng* using one or more of the following markers: serum creatinine, serum urea, creatinine clearance, glomerular filtration rate, albuminuria, or proteinuria. In the second stage, the pre-selected articles were read in full to determine their inclusion based on the eligibility criteria. A flowchart was then created, illustrating the number of articles included and excluded at each stage according to the eligibility criteria, in accordance with the PRISMA recommendation (2020).

Data Extraction from Selected Articles

Only preclinical trials were found in the selected databases. From the selected pre-clinical trials, the following data were extracted for table construction: administered dose of *Panax notoginseng*, route of administration, part of the plant used, duration of treatment, plant component used, type of mouse, sample size of the intervention group and control group, animal model of nephropathy (chronic kidney disease, diabetic kidney disease, hypertensive nephropathy, acute kidney injury, kidney injury induced by nephrotoxic drugs), method of inducing nephropathy, biochemical markers used to evaluate the nephroprotective effect (creatinine, urea, glomerular filtration rate, creatinine clearance, proteinuria, albuminuria), and the results obtained.

Assessment of the Quality of Studies

The quality of the pre-clinical trials included in the systematic review was assessed independently by two reviewers using the SYRCLE tool, which evaluates the following categories: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. Ten questions were applied to the articles included in the systematic review, with responses categorized as “YES,” indicating a low risk of bias; “NO,” indicating a high risk of bias; and “UNCERTAIN,” indicating an unclear risk of bias. It is not recommended to calculate the sum score of each individual study using this tool[11].

RESULTS

The article selection steps are summarized in a flowchart (Figure 1). In this systematic review, 14 articles were included after evaluating all eligibility criteria.

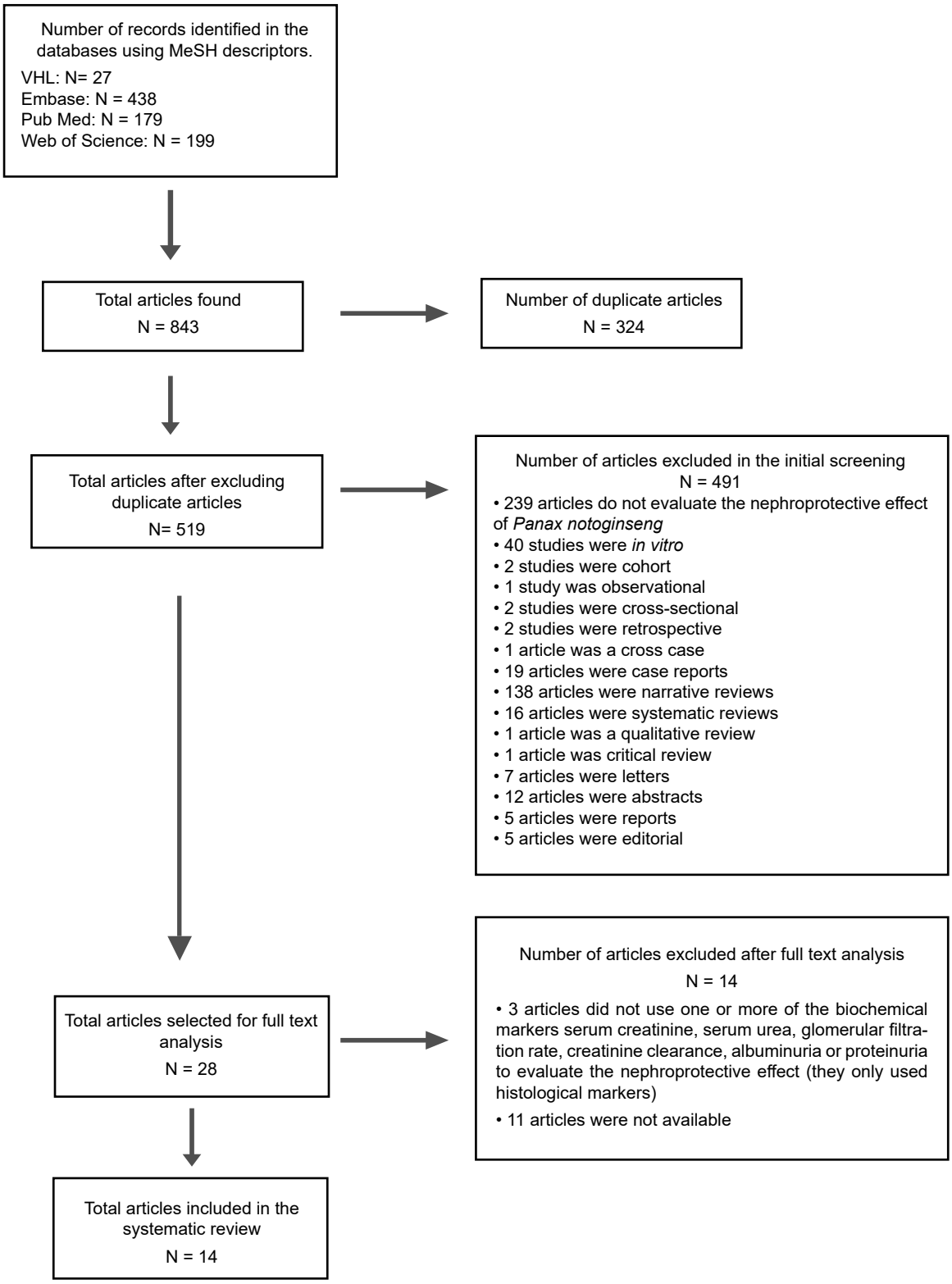

FIGURE 1. Flowchart of the selection of articles that evaluated the nephroprotective effect of *Panax notoginseng* that were included in the systematic review according to the eligibility criteria used in the study.

Table 1 presents the characteristics of the selected studies, which were published between 2000 and 2021.

TABLE 1. Characteristics of preclinical studies that evaluated the nephroprotective effect of *Panax notoginseng* and that were included in the systematic review.

Author/ Year	Plant component used	Route of administration	Dose administered	Type of animal	Size of control group and intervention group	Duration of treatment
Guo *et al*., 2021	Panaxydiol	NI	10 e 20 mg/ Kg	Male Wistar rats	CG: 6, IG: 6	20 days
Xie *et al*., 2020	Crude extract	Oral	400 mg/kg	Male Sprague-Dawley rats	CG: 7, IG: 7	84 days
Xue *et al*., 2020	Saponins	Intragastric	5 mg/Kg	Male Sprague-Dawley rats	CG: 8, IG: 8	84 days
Zhai *et al*., 2019	Crude extract	NI	400 mg/Kg	Male Sprague-Dawley rats	CG: 6, IG: 6	84 days
Zhang, Y. *et al*., 2019	Saponins	Intramuscular injection	10 mg/Kg 2 vezes ao dia	ICR mice	CG: 6, IG: 6	14 days
Li *et al*., 2019	Crude extract	Oral	NI	Male Sprague-Dawley rats	CG: 8, IG: 2 groups with 8	63 days
Zhang, B. *et al*., 2019	Notoginsenoside R1	Intragastric	30 mg/Kg	Female C57BL/KsJ db / db mice and C57BL/6J mice	CG: 8, IG: 8	140 days
Liang *et al*., 2017	Saponins	Injection into the abdominal cavity	31,35 mg/ Kg	Male Sprague-Dawley rats	CG: 6, IG: 6	3 days
Du *et al*., 2016	Saponins	Intragastric	100 e 200 mg/Kg	Male Sprague-Dawley rats	CG: 10, IG: 2 groups with 10	90 days
Liu *et al*., 2014	Saponins	Intraperitoneal injection	31,35 mg/ Kg	Male Sprague-Dawley rats	CG: 12, IG: 12	8 days
Tu; Dong; Lu, 2011	Notogynoside	Oral	100 e 200 mg/Kg	Male Sprague-Dawley rats	CG: 10, IG: 2 groups with 10	28 days
Tu *et al*., 2011	Notogynoside	Intragastric	100 e 200 mg/kg	Male Wistar rats	CG: 10, IG: 2 groups with 10	42 days
Liu *et al*., 2010	Notoginsenoside R1	Intraperitoneal injection	20 e 40 mg/ Kg	Male Sprague-Dawley rats	CG: 6, IG: 2 groups with 6	3 days
Liu; Zhou, 2000	Saponins	Intraperitoneal injection	50, 100 e 200 mg/Kg	Kunming mice	CG: 8, IG: 3 groups with 8	2 days

NI: not informed; CG: control group; IG: intervention group (received *Panax notoginseng* components).

The substances used were taken from *Panax notoginseng* or derivatives, in doses ranging from 5 mg/kg to 400 mg/kg, and were administered intraperitoneally in four studies[12-13-14-15] (28.6%), intragastrically in four studies[16-17-18-19] (28.6%), oral in three studies[7-20-21] (21.4%), intramuscular in one study[9] (7.1%) and two studies did not inform the route of administration[22-23] (14.3%).

Regarding the plant components used, six studies[9-12-13-15-16-17] (42.9%) used total saponins from *Panax notoginseng*, three analyzed the crude extract[7-21-23] (21.4%), two notoginsenoside[18-20] (14.3%), another two notoginsenoside R1[14-19] (14.3%), and one used panaxydiol[22] (7.1%).

All studies were pre-clinical trials and used animals for testing. Nine studies[7-12-13-14-16-17-20-21-23] (64.3%) used male Sprague-Dawley rats; two[18-22] (14.3%) male Wistar rats; one[9] (7.1%) female ICR mice; one[19] (7.1%) female C57BL/KsJ db / db mice; one[15] (7.1%) Kunming mice. Treatment time in the studies varied between 2 and 140 days, with control and intervention group sizes varying between 6 and 12 animals.

Table 2 presents the animal model of nephropathy, biochemical markers used to evaluate the nephroprotective effect and the results obtained.

TABLE 2. Animal model and method of inducing nephropathy, biochemical markers for evaluating renal function and results obtained from preclinical studies that evaluated the nephroprotective effect of *Panax notoginseng* and that were included in the systematic review.

Author/Year	Animal model of nephropathy/ Method of inducing nephropathy	Biochemical markers for assessing renal function	Result obtained
Guo *et al*., 2021	AKI induced by nephrotoxic substance/ Aristolochic acid administration	Proteinuria, serum creatinine, serum urea	There was a significant reduction in 24 hour urine proteinuria and serum creatinine and urea levels in IGs who received 10 and 20 mg/kg/day of panaxydiol compared to the CG ($p < 0.05$).
Xie *et al*., 2020	DKD/ Streptozotocin administration	Albuminuria, serum creatinine	There was a significant reduction in urinary ACR in the IG compared to the CG ($p < 0.05$) after 3 and 12 weeks. There was no significant difference between the groups regarding serum creatinine levels.
Xue *et al*., 2020	DKD/ Streptozotocin administration	Albuminuria, serum creatinine, serum urea	There was a significant reduction in urinary ACR in the IG compared to the CG ($p < 0.05$) after 6 and 12 weeks. There was no significant difference in serum urea and creatinine levels.
Zhai *et al*., 2019	DKD/ Streptozotocin administration	Albuminuria, serum creatinine	There was a significant reduction in urinary ACR in the IG compared to the CG ($p < 0.05$) after 3 and 12 weeks. There was no significant difference between the groups regarding serum creatinine levels.
Zhang, Y. *et al*., 2019	AKI induced by nephrotoxic substance/ Polymyxin E administration	Serum creatinine, serum urea	There was a significant reduction in serum creatinine and urea levels in the IG compared to the CG ($p < 0.05$).
Li *et al*., 2019	DKD/ Streptozotocin administration	Proteinuria, serum creatinine, serum urea	There was a significant reduction in proteinuria and serum creatinine and urea levels in IGs who received low and high doses of *Panax notoginseng* compared to the CG ($p < 0.05$).
Zhang, B. *et al*., 2019	DKD/ Transgenic mice models of T2DM	Albuminuria, serum creatinine, serum urea	There was a significant reduction in albuminuria and serum creatinine ($p < 0.01$) and urea ($p < 0.05$) levels in the IG group compared to the CG.

Liang *et al*., 2017	AKI induced by nephrotoxic medication/ Cisplatin administration	Serum creatinine, serum urea	There was a significant reduction in serum creatinine and urea levels in the IG compared to the CG ($p < 0.05$) after 24 and 72 hours.
Du *et al*., 2016	DKD/ Alloxan administration	Proteinuria, serum creatinine, serum urea	There was a significant reduction in proteinuria and serum creatinine and urea levels in IGs that received 100 and 200 mg/kg/day of *Panax notoginseng* compared to the CG ($p < 0.01$).
Liu *et al*., 2014	AKI induced by nephrotoxic medication/ Cisplatin administration	Serum creatinine, serum urea	There was a significant reduction in serum creatinine and urea levels in the IG compared to the CG ($p < 0.01$) after 1, 4 and 8 days.
Tu; Dong; Lu, 2011	DKD/ Streptozotocin administration	Albuminuria, serum creatinine, creatinine clearance	There was a significant reduction in albuminuria in IGs that received 100 mg/kg/day (1.06 ± 0.10 µg/mL) and 200 mg/kg/day (0.97 ± 0.07 µg/mL) of notoginsenoside compared to the CG (2.66 ± 0.35 µg/mL) ($p < 0.01$). There was a significant reduction in serum creatinine in IGs that received 100 mg/kg/day (130.85 ± 6.84 µmol/L) and 200 mg/kg/day (109.69 ± 9.51 µmol/L) of notoginsenoside compared to the CG (165.32 ± 12.37 µmol/L) ($p < 0.05$ and $p < 0.01$, respectively). There was a significant increase in creatinine clearance in IGs that received 100 mg/kg/day (5.03 ± 0.58 mL/min) and 200 mg/kg/day (4.09 ± 0.67 mL/min) of notoginsenoside compared to the CG (6.13 ± 0.37 mL/min) ($p < 0.05$ and $p < 0.01$, respectively).
Tu *et al*., 2011	DKD/ Streptozotocin administration	Creatinine clearance, albuminuria	There was a significant reduction in albuminuria in IGs that received 100 mg/kg/day (27.94 ± 8.38 µg/24h) and 200 mg/kg/day (27.43 ± 11.26 µg/24h) of notoginsenoside compared to the CG (40.93 ± 5.42 µg/24h) ($p < 0.01$). There was a significant increase in creatinine clearance in IGs that received 100 mg/kg/day (6.75 ± 1.59 mL/min/kg) and 200 mg/kg/day (5.91 ± 1.67 mL/min /kg) of notoginsenoside compared to the CG (8.50 ± 0.71 mL/min/kg) ($p < 0.01$).
Liu *et al*., 2010	AKI ischemia-induced/ Interruption of renal blood flow	Serum creatinine	There was a significant reduction in serum creatinine levels in IGs that received 20 and 40 mg/kg/day compared to the CG ($p < 0.05$).
Liu; Zhou, 2000	AKI induced by nephrotoxic medication/ Cisplatin administration	Serum creatinine, serum urea	There was a significant reduction in serum creatinine levels in IGs that received 50 mg/kg/day (303 ± 49 µmol/L), 100 mg/kg/day (246 ± 29 µmol/L) and 200 mg/kg/day (120 ± 18 µmol/L), compared to the GC (284 ± 18 µmol/L) ($p < 0.01$). There was a significant reduction in serum urea levels in IGs that received 50 mg/kg/day (40 ± 2 mmol/L), 100 mg/kg/day (30 ± 3 mmol/L) and 200 mg/kg/day (11 ± 1 mmol/L), compared to the GC (36 ± 6 mmol/L) ($p < 0.01$).

T2DM = type 2 diabetes mellitus; DKD: Diabetes kidney disease; AKI = acute kidney injury; ACR = albumin/creatinine ratio; CG: control group; IG: intervention group (received *Panax notoginseng* components).

Among the selected studies, eight[7-16-17-18-19-20-21-23] (57.1%) evaluated diabetic kidney disease; five[9-12-13-15-22] (35.7%) analyzed acute kidney injury induced by nephrotoxic substances; one[14] (7.1%) evaluated acute kidney injury induced by ischemia. Several methods were used to induce nephropathies, six studies[7-17-18-20-21-23] (42.9%) administered streptozotocin; three[12-13-15] (21.4%) administered cisplatin, one[22] (7.1%) administered aristolochic acid; one[9] (7.1%) polymyxin E; one[16] (7.1%) alloxan; one[19] (7.1%) used transgenic mice model of type 2 diabetes mellitus; one[14] (7.1%) underwent surgical ischemia.

Among the eight studies that used the animal model of diabetes kidney disease, seven[7-16-17-19-20-21-23] (87.5%) evaluated serum creatinine levels, and among these, four[7-16-19 -20] (57%) observed that creatinine levels reduced significantly after treatment, the other three[17-22-24] (43%) did not observe a significant difference. Three[16-19-23]

(37.5%) studies evaluated serum urea levels, among these, two[16-19] (67%) found a reduction in urea levels after treatment, and one[23] (33%) did not observe a significant difference between the intervention and control groups. Three[18-19-20] (37.5%) studies evaluated albuminuria, and all of them (100%) reported that there was a significant decrease in albuminuria after treatment. Three studies[17-21-23] (37.5%) evaluated the albumin/creatinine ratio (ACR), and all of them (100%) observed that there was a significant reduction in this marker after treatment. Two studies[7-16] (25%) evaluated proteinuria, and a significant reduction in the levels of this marker was observed after treatment in both (100%). Two studies[18-20] (25%) evaluated creatinine clearance, and both (100%) found an increase in creatinine clearance after treatment with *Panax notoginseng*.

Among the three studies[12-13-15] that evaluated cisplatin induced nephropathy, all of them (100%) evaluated serum creatinine and urea levels and observed that the levels of these markers reduced after treatment.

The study[9] that evaluated polymyxin E induced nephropathy observed that serum creatinine and urea levels reduced after treatment. Another study[22] that evaluated nephropathy induced by the administration of aristolochic acid found that proteinuria, serum creatinine and serum urea reduced after treatment. Finally, the study[14] that evaluated ischemia induced nephropathy observed that serum creatinine levels reduced after treatment.

Among the fourteen studies selected, only three[15-18-20] presented mean and standard deviation values, and only two[18-20] used the same animal model of nephropathy (diabetic kidney disease). Although these two studies evaluated albuminuria and creatinine clearance, they used different measurement units that cannot be converted into one another, which made meta-analysis unfeasible.

Table 3 presents the results for the methodological quality of the articles assessed using the SYRCLE scale.

TABLE 3. Assessment of the quality of studies according to the SYRCLE tool.

Author/Year	Selection Bias			Performance Bias		Detection Bias		Attrition Bias	Reporting Bias	Other Sources of Bias
	1	2	3	4	5	6	7	8	9	10
Guo et al., 2021	L	L	H	L	H	H	H	L	L	?
Xie et al., 2020	L	L	H	L	H	H	H	L	L	L
Xue et al., 2020	L	L	H	L	H	H	H	L	L	L
Zhai et al., 2019	L	L	H	L	H	H	H	L	L	L
Zhang, Y. et al., 2019	L	L	H	L	H	H	H	L	L	L
Li et al., 2019	?	L	H	L	H	H	H	L	L	L
Zhang, B. et al., 2019	L	L	H	L	H	H	H	L	L	L
Liang et al., 2017	L	L	H	L	H	H	H	?	L	L
Du et al., 2016	L	L	H	L	H	H	H	L	L	L
Liu et al., 2014	?	L	H	L	H	H	H	L	L	L
Tu; Dong; Lu, 2011	L	L	H	L	H	H	H	L	L	?
Tu et al., 2011	L	L	H	L	H	H	H	L	L	?
Liu et al., 2010	L	L	H	L	H	H	H	L	L	L
Liu; Zhou, 2000	L	L	H	L	H	H	H	L	L	?

L – Low risk of bias; H – high risk of bias; ?– uncertain risk of bias

1- Allocation series: Random distribution of the control and intervention groups (which received *Panax notoginseng*) in twelve articles, the remaining two presented uncertainty regarding the distribution 2- Base characteristic: Both the intervention group and the control group presented nephropathy in all articles; 3- Concealment of allocation: It was not reported in any article whether there was concealment in the designation of the control and intervention groups; 4- Random accommodation: The distribution of the control and intervention groups occurred randomly between the accommodations and they were subjected to the same conditions in all articles; 5- Blinding: It was not described in any article whether the researcher was aware of which animals received *Panax notoginseng* or placebo; 6- Random assessment of the outcome: No article reported whether the analysis of the outcome of the control and intervention groups was carried out randomly; 7- Blinding: It was not reported in any article whether the researchers knew which animals had received *Panax notoginseng* or placebo in evaluating the outcome; 8- Incomplete outcome result: In thirteen articles the outcome presented the same number of animals present at the beginning of the study and in one article it was not specified whether the same number of animals were used at the beginning of the study and at the outcome; 9- Selective reporting of the outcome: There was no selective reporting of the outcome for results that were significant in any article because all results were described; 10- Other sources of bias/conflict of interest between the authors: There was no conflict of interest between the authors in ten articles, and it was not specified whether there was a conflict of interest between the authors in four articles.

Regarding the criteria for evaluating the quality of studies, in terms of selection bias, twelve articles[9-12-14-15-16-17-18-19-20-21-22-23] (85.71%) presented a low risk of bias regarding the allocation series, and two[7-13] (14.28%) presented uncertainty regarding the distribution, configuring an uncertain risk of bias; all studies had a low risk of bias for the base characteristic; and all of them presented high risk of bias for allocation concealment. In terms of performance bias, all studies presented a low risk of bias in relation to random accommodation; no study described whether there was blinding regarding the researcher's knowledge regarding the animals that received placebo or *Panax notoginseng*, configuring a high risk of bias. In terms of detection bias, all studies presented a high risk of bias for random assessment of the outcome and blinding in the assessment of the outcome. Only one study[12] (7.14%) presented a high risk of bias in terms of attrition bias, in the incomplete outcome criteria, as it was not specified whether the same number of animals were used at the beginning of the study and at the outcome. The other thirteen studies[7-9-13-14-15-16-17-18-19-20-21-22-23] (92.86%) presented a low risk of bias in the incomplete outcome criteria. Regarding reporting bias, all studies presented a low risk of bias, as did ten studies in the assessment of other sources of bias, as no conflict of interest was observed between the authors, and an uncertain risk for four studies, as they did not present the declaration of conflict of interest.

DISCUSSION

All preclinical studies evaluated in this systematic review demonstrated that *Panax notoginseng* has a nephroprotective effect when used in the treatment of nephropathies in animal models. Although three studies17-21-23 did not observe a reduction in serum creatinine levels and one of these studies17 did not find a significant reduction in serum urea levels, all three studies did find a significant decrease in albuminuria in animals treated with *Panax notoginseng*, indicating its nephroprotective effect.

The nephroprotective effect of *Panax notoginseng* in animals with diabetic kidney disease was evaluated in eight studies included in this systematic review. Diabetic kidney disease is a microvascular complication of diabetes mellitus20, which is diagnosed by increased albuminuria and/or reduced glomerular filtration rate24. One of the main mechanisms of this nephropathy is the irreversible non-enzymatic glycation of proteins, lipids, or nucleic acids, resulting in the formation of advanced glycation end products (AGEs). The concentration of glucose is closely related to the formation of AGEs, and hyperglycemia accelerates this process25. AGEs are deposited in the glomerular wall, exerting harmful effects, bypassing the microcirculation of the glomerulus, and promoting the development of proteinuria26. At a cellular level, AGEs activate AGE receptors (RAGE), inducing intracellular signaling that generates oxidative stress and increases the production of pro-inflammatory cytokines25. Some studies have found that *Panax notoginseng* can reduce the production of AGEs, oxidative stress, apoptosis, podocyte dysfunction, renal fibrosis, and the production of inflammatory cytokines16-19-20-21. This decrease in AGEs production is associated with the ability of *Panax notoginseng* to reduce glycemia, thereby reducing irreversible non-enzymatic glycation and the formation of AGEs7.

Oxidative stress is associated with several events in the pathophysiology of diabetic kidney disease and drug- or ischemia-induced acute kidney injury. Caused by a significant increase in reactive oxygen species (ROS) promoted by AGEs through the activation of NADPH oxidase (Nox4) in diabetic kidney disease, and by an imbalance in ROS and antioxidants in acute kidney injury, oxidative stress induces the production of extracellular matrix, resulting in the thickening of the renal glomerular basal membrane, proliferation of mesangial cells, and podocyte apoptosis, increasing the chances of developing renal fibrosis19.

Antioxidants are one of the defense mechanisms against oxidative stress based on the clearance of ROS. Some studies have demonstrated the antioxidant effect of *Panax notoginseng* by positively regulating the levels of several proteins with antioxidant functions capable of interacting with ROS, thus preventing oxidative stress7-9-16-23. The enzyme superoxide dismutase (SOD) is composed of proteins and catalytic ions and reduces oxidative stress by removing endogenous or exogenous superoxide radicals9. The mechanism behind the positive regulation of SOD is associated with the silent information regulator 1 (SIRT1), which, in the presence of increased glucose concentrations, is reduced. Conversely, treatment with *Panax notoginseng* increases SIRT1, which activates antioxidant proteins and positively regulates SOD16.

A mechanism presented in the study by Liang et al.12 to combat oxidative stress due to cisplatin-induced nephrotoxicity was the renal cell autophagy response. The study demonstrated that *Panax notoginseng* increases mitophagy through the HIF-1α/BNIP3/Beclin-1 pathway, maintaining functional mitochondria by degrading only damaged mitochondrial components, DNA, and membranes. Following treatment with *Panax notoginseng* after cisplatin-induced acute kidney injury, the expression of HIF--1α, a transcription factor that transcribes BNIP3 and other genes at the nuclear level, is elevated. Increased expression of BNIP3 stimulates mitophagy, preventing the binding of Bcl-2 to Beclin-1, which stimulates the autophagy process12.

The nephroprotective effect of *Panax notoginseng* can also be explained by its antiapoptotic effect due to its action on the Bax/Bcl-2 pathway9-13-14-19-23. In podocytes affected by oxidative stress, activation of the pro-apoptotic protein Bax occurs, which accumulates in mitochondria and increases the permeability of the mitochondrial outer membrane, resulting in the release of cytochrome C that initiates the mitochondrial pathway of apoptosis (intrinsic pathway) by combining with the cytoplasmic protein Apaf-1 and the caspase-9 precursor enzyme to activate the caspase-9 cascade. In contrast, the anti-apoptotic protein Bcl-2 inhibits Bax and ensures mitochondrial membrane integrity. Under oxidative stress, Bcl-2 is inactivated by forming heterodimers with Bax, which is at increased levels. Therefore, the Bax/Bcl-2 ratio is altered, leading to mitochondrial membrane permeabilization and apoptosis of renal cells. The anti-apoptotic effect of *Panax notoginseng* is reported to occur through upregulation of Bcl-2 and downregulation of Bax14.

Inflammation is a significant pathophysiological component of acute kidney injury and diabetic kidney disease, characterized by increased expression of the pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-α), which positively regulates other pro-inflammatory cytokines

and chemokines14-16. A key mechanism behind TNF-α's pathophysiology is its ability to activate the nuclear factor κB (NF--κB) pathway, a family of inducible transcription factors, with its activation being a crucial event in signaling for the induction of inflammatory gene expression28. Some studies16-14 described that *Panax notoginseng* has anti-inflammatory activity by inhibiting TNF-α and negatively regulating the activation of NF-κB.

Thus, *Panax notoginseng* presents a significant nephroprotective effect in preclinical trials due to its hypoglycemic, anti-inflammatory, and antioxidant properties, among others, highlighting the need for clinical trials to confirm these beneficial effects in humans. Currently, the treatment of diabetic kidney disease, as described by the American Diabetes Association (2022)24, primarily involves non-pharmacological recommendations and the use of nephroprotective medications such as ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which can, in many patients, prevent progression to more advanced stages of kidney disease. Therefore, there is a limitation in the existing drug options for pharmacological treatment, making the use of *Panax notoginseng* promising as an adjunct in treatment.

Moreover, many effective medicines for various diseases have limited clinical use due to nephrotoxicity as an adverse reaction. Some studies9-12-13-28 have shown that *Panax notoginseng* may be beneficial in these situations due to its ability to prevent nephrotoxicity caused by potentially nephrotoxic medications, such as polymyxin E (an antibiotic) and cisplatin (a chemotherapy drug). Therefore, the concurrent use of *Panax notoginseng* with potentially nephrotoxic medications has intriguing clinical applications. It is crucial that clinical trials are conducted to verify the nephroprotective effect of *Panax notoginseng* so it can be used to prevent nephrotoxic adverse reactions caused by certain drugs.

Regarding the safety of using *Panax notoginseng*, some studies17-21-23 found no renal or hepatic toxicity. In a clinical trial by Nomura et al. (2013)29, a damarane--type triterpene extract tablet, a modified compound of saponins extracted from the roots of *Panax notoginseng*, was tested. Individuals who received this treatment for sixteen weeks showed no changes in relevant hematological and biochemical parameters nor adverse effects, making its use as a nephroprotective agent very attractive. Adverse reactions related to the use of *Panax notoginseng* are mainly associated with misuse or overdose, leading to symptoms such as nausea, vomiting, and epistaxis30.

In the studies included in this systematic review, various components and doses of *Panax notoginseng* were used. Such variations in dosage may be related to the assessment of toxicity and pharmacological safety, as outlined by Anvisa (2013)31. Additionally, there was variation between studies regarding the route of administration, duration of treatment, type of animal used, and method of inducing nephropathy. This heterogeneity among studies constitutes a limitation of this systematic review. Other limitations include the infeasibility of conducting a meta-analysis, the absence of clinical trials on the topic, and the high risk of bias presented by some studies in the assessment of methodological quality.

On the other hand, this systematic review is highly relevant, as it included a significant number of studies, and most results were consistent, observing a reduction in bio-

chemical markers for assessing renal function following treatment with *Panax notoginseng*. This supports the inference that *Panax notoginseng* has a nephroprotective effect in various animal models of nephropathy.

CONCLUSION

This systematic review concludes that *Panax notoginseng* exhibits a nephroprotective effect in various animal models of nephropathy, including diabetic kidney disease, kidney injury induced by nephrotoxic substances, and ischemia. Given this, the clinical use of *Panax notoginseng* appears promising, as its pharmacological potential may offer an alternative or adjunct to current pharmacotherapy for renal dysfunction and in the prevention of drug-induced nephrotoxicity. Therefore, clinical trials are necessary to validate the effectiveness of *Panax notoginseng* as a nephroprotective agent in humans.

BIBLIOGRAPHIC REFERENCES

1. Tang X, Huang M, Jiang J, Liang X, Li X, Meng R, et al. Panax notoginseng preparations as adjuvant therapy for diabetic kidney disease: a systematic review and meta-analysis. Pharm Biol. 2020; 58:138–45.
2. Zhang X, Zhou C, Miao L, et al. Panax Notoginseng Protects against Diabetes-Associated Endothelial Dysfunction: Comparison between Ethanolic Extract and Total Saponin. Oxid Med Cell Longev 2021; 2021:4722797. 10.1155/2021/4722797
3. Liu HB, Lu XY, Hu Y, Fan XH. Chemical constituents of Panax ginseng and Panax notoginseng explain why they differ in therapeutic efficacy. Pharmacol Res. 2020; 161:105263.
4. Chen Z, Li J, Liu J, Zhao Y, Zhang P, Zhang M, Zhang L. Saponins isolated from the root of Panax notoginseng showed significant anti-diabetic effects in KK-Ay mice. Am. J. Chin. Med. 2008; 36: 939-951.
5. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022;102(5S): S1–S127.
6. Sá J, Canani L, Rangel E, Bauer A, Escott G, Zelmanovitz T, Silveiro S, Bertoluci M. Doença renal do diabetes. Diretriz Oficial da Sociedade Brasileira de Diabetes (2022). DOI: 10.29327/557753.2022-18, ISBN: 978-65-5941-622-6.
7. Li J, Qiu P, Wang S, Wu J, He Q, Li K, et al. β-N-Oxalyl-L-α,β-diaminopropionic acid from Panax notoginseng plays a major role in the treatment of type 2 diabetic nephropathy. Biomed. Pharmacother. 2019; 114:108801. doi: 10.1016/j.biopha.2019.108801
8. Perazella MA. Pharmacology behind common drug nephrotoxicities. Clin J Am Soc Nephrol 2018; 13: 1897–1908
9. Zhang Y, Chi X, Wang Z, et al. Protective effects of Panax notoginseng saponins on PME-Induced nephrotoxicity in mice. Biomed Pharmacother. 2019; 116:108970.
10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71
11. Hooijmans C, Rovers M, De Vries R, Leenaars M, Ritskes-Hoitinga M, Lan-

gendam M. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014; 14:1-9.
12. Liang X, Yang Y, Huang Z, Zhou J, Li Y, Zhong X. Panax notoginseng saponins mitigate cisplatin induced nephrotoxicity by inducing mitophagy via HIF-1alpha. Oncotarget. 2017;8:102989–3003.
13. Liu X, Huang Z, Zou X, Yang Y, Qiu Y, Wen Y. Panax notoginseng saponins attenuates cisplatin-induced nephrotoxicity via inhibiting the mitochondrial pathway of apoptosis. Int. J. Clin. Exp. Pathol. 2017; 7(12): 8391-8400.
14. Liu WJ, Tang HT, Jia YT, Ma B, Fu JF, Wang Y, Lv KY and Xia ZF: Notoginsenoside R1 attenuates renal ischemia-reperfusion injury in rats. Shock. 2010; 34:314–320.
15. Liu SJ, Zhou SW. Panax notoginseng saponins attenuated cisplatin-induced nephrotoxicity. Acta Pharmacol. 2000; 21(3): 257-260
16. Du YG, Wang LP, Qian JW, Zhang KN, Chai KF. Panax notoginseng saponins protect kidney from diabetes by up-regulating silent information regulator 1 and activating antioxidant proteins in rats. Chin. J. Integr. Med. 2016; 22: 910–917
17. Xue R, Zhai R, Xie L, Zheng Z, Jian G, Chen T, Su J, Gao C, Wang N, Yang X, Xu Y, Gui D. Xuesaitong protects podocytes from apoptosis in diabetic rats through modulating PTEN-PDK1-Akt-mTOR Pathway. J Diabetes Res. 2020;12.
18. Tu Q, Qin J, Dong H, Lu F, Guan W. Effects of Panax notoginoside on the expression of TGF-β1 and Smad-7 in renal tissues of diabetic rats. J Huazhong Univ Sci Technolog Med Sci. 2011; 31:190–193. doi: 10.1007/s11596-011-0250-5.
19. Zhang B, Zhang X, Zhang C, Shen Q, Sun G, Sun X. Notoginsenoside R1 Protects db/db Mice against Diabetic Nephropathy via Upregulation of Nrf2-Mediated HO-1 Expression. Molecules. 2019; 24(247).
20. Tu QN, Dong H, Lu FE. Effects of panax notoginoside on the nephropathy in rats with type 1 diabetes mellitus. Chin J Integr Med. 2011;17:612–615.
21. Xie L, Zhai R, Chen T, Gao C, Xue R, Wang N, et al. Panax Notoginseng Ameliorates Podocyte EMT by Targeting the Wnt/β-Catenin Signaling Pathway in STZ-Induced Diabetic Rats. Drug Design Dev Ther. 2020;14:527–538.
22. Guo Y, Hu M, Ma J, Chinnathambi A, Alharbi SA, Shair OHM, et al. Protective effect of panaxydol against repeated administration of aristolochic acid on renal function and lipid peroxidation products via activating Keap1-Nrf2/ARE pathway in rat kidney. J Biochem Mol Toxicol. 2020;35:e22619.
23. Zhai R, Jian G, Chen T, Xie L, Xue R, Gao C, Wang N, Xu Y, Gui D (2019) Astragalus membranaceus and Panax notoginseng, the novel renoprotective compound, synergistically protect against podocyte injury in streptozotocin-induced diabetic rats. J Diabetes Res. 2019; 1:1–14.
24. American Diabetes Association. Standards of medical care in diabetes—2021. Diabetes Care. 2021;45.
25. Burtis C, Ashwood E, Bruns D. Tietz Fundamentos de Química Clínica. 6. ed. Rio de Janeiro: Elsevier, 2008.
26. Sociedade Brasileira De Diabetes (BR); Sociedade Brasileira De Endocrinologia E Metabologia (BR); Sociedade Brasileira De Nefrologia (BR). Posicionamento Oficial Tripartite nº 01/2016 SBD / SBEM / SBN: PREVENÇÃO, DI-

AGNÓSTICO E CONDUTA TERAPÊUTICA NA DOENÇA RENAL DO DIABETES. 2016; 01/2016:100.

27. Hayden M, Ghosh S. Regulation of NF-κB by TNF family cytokines. Semin. Immunol. 2014; 26(3): 253–266.
28. Li Q, Liang X, Yang Y, Zeng X, Zhong X, Huang C. *Panax notoginseng* saponins ameliorate cisplatin-induced mitochondrial injury via the HIF-1alpha/mitochondria/ROS pathway. FEBS Open Bio. 2020; 10: 118–126.
29. Nomura M, Iwasaki H, Suzuki N, Murata A, Iwamoto T, Kitamura K, Takamura Y, Koide M, Murakoshi M, Nishino H. Potent Anti-Hyperglycemic Effects of Panax Notoginseng Extract Containing Dammarane-Type Triterpenes in Human Subjects. CLINICAL THERAPEUTICS/NEW TECHNOLOGY—GLUCOSE MONITORING AND SENSING: ADA-Funded Research, Diabetes Journal. 2013; 62: A296-A297.
30. Wang T, Guo R, Zhou G, Zhou X, Kou Z, Sui F, et al. Traditional uses, botany, phytochemistry, pharmacology and toxicology of Panax notoginseng (Burk.) FH Chen: a review. J Ethnopharmacol. 2016;188:234–58.
31. AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA (BR). Guia para a condução de estudos não clínicos de toxicologia e segurança farmacológica necessários ao desenvolvimento de medicamentos. GESEF. 2nd ed. Brasília; 2013. 48 p.

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