Heliyon 10 (2024) e24119

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

The pharmacology activities of *Angelica keiskei* Koidzumi and its efficacy and safety in humans

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ARTICLE INFO

Keywords:
Antioxidants
4-Hydroxyderricin
Japanese celery
Quality of life
Xanthoangelol

ABSTRACT

Chronic exposure to elevated levels of pro-oxidant factors may cause structural failings at the mitochondrial DNA level and alteration of antioxidant enzymes (glutathione peroxidase, catalase, and superoxide dismutase). Oxidative stress is an imbalance between the capacity of endogenous non-enzymatic antioxidants (glutathione, alpha-lipoic acid, uric acid, ferritin, metallothionein, melatonin, and bilirubin) and the occurrence of pro-oxidant factors which may lead to the pathogenesis of various diseases that affects the kidneys, pancreas, central nervous system, and cardiovascular system. Therefore, the utilization of medicinal plants with antioxidant activity, e.g., *Angelica keiskei* Koidzumi which contains chalcones, is interesting to be explored. Chalcones exhibit direct and indirect antioxidant activity and prevent oxidative stress by decreasing ROS, RNS, and superoxide production. In this review, we discuss the pharmacology activities of *A. keiskei* Koidzumi and its efficacy in humans. The articles were explored on PubMed and Google Scholar databases and based on the titles and abstracts related to the topic of interest, and 55 articles were selected. Two main chalcones of this plant, 4-hydroxyderricin and xanthoangelol, have been reported for their various pharmacology activities. The efficacy of *A. keiskei* was confirmed in anti-obesity, hepatoprotective, anti-diabetes mellitus, and increasing plasma antioxidants in patients with metabolic syndrome. *A keiskei* is safe as proven by only mild or no adverse events reported, thus it is prospective to be further developed as an antioxidant nutraceutical.

1. Introduction

Oxidative stress is a disturbance in the balance of pro-oxidants and antioxidants that is caused by the formation of reactive oxygen (ROS) and reactive nitrogen species (RNS) [1,2]. Excessive amounts of ROS and RNS may lead to the oxidation of biological molecules such as lipids, proteins, and deoxyribonucleic acid (DNA) [1]. The elevation of ROS production is induced by ultraviolet radiation, pollutants, or heavy metals exposure [3]. Oxidative stress may lead to the pathogenesis of various diseases, e.g., acute kidney injury,

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https://doi.org/10.1016/j.heliyon.2024.e24119
Received 21 June 2023; Received in revised form 3 January 2024; Accepted 3 January 2024
Available online 13 January 2024

atherosclerosis, obstructive pulmonary disease, Alzheimer's, diabetes mellitus, neurodegenerative diseases, cancer, inflammation, and cardiovascular disease [4–7]. Endogenous antioxidants such as glutathione, alpha-lipoic acid, uric acid, ferritin, metallothionein, melatonin, and bilirubin are effective in blocking the harmful effects of ROS, however, their amounts are sometimes not sufficient [8–10]. Therefore, exogenous antioxidants, particularly those derived from medicinal plants, are needed [11,12].

The utilization of medicinal plants with antioxidant activity, e.g., *Angelica keiskei* Koidzumi which contains chalcones, is interesting to be explored. *A. keiskei* (family Apiaceae) has shown a strong antioxidant activity [13–15]. The fresh leaves of this plant can be devoured directly without prior processing [16], because of their sweet, slightly bitter astringent taste, combined with a fragrant aroma [17]. The stem of *A. keiskei* contains a yellow sap, with an abundant capacity of chalcones (e.g., xanthoangelol and 4-hydroxyderricin), that are not found in another genus of *Angelica* plants [18]. Xanthoangelol (XA) has been determined in the leaf extract *A. keiskei* with a concentration of 1.959 % [19]. The chalcones compounds of *A. keiskei* have been reported for their various pharmacological activities, including nephroprotective effects, anti-obesity, anti-diabetic, anti-inflammatory, hepatosteatosis, antituberculosis, antitumor, and antimetastatic [20–31]. However, it is interesting to further explore the pharmacology activities by *in silico, in vitro*, and *in vivo* studies of *A. keiskei* and its efficacy to humans which support the potential of *A. keiskei* as herbal medicine. In this paper, we summarized the parts of the plant that have been tested for their pharmacological activities to combat diseases triggered by oxidative stress such as kidney disease, liver injury, obesity, diabetes mellitus, cardiovascular disease, inflammation, myopathy, and neurotoxicity damage. Through this review, readers will get insights about the benefits and safety of *A. keiskei* in humans, particularly from the pharmacology perspectives.

2. Methods

This review was based on the article published during 2012–2022 and included publications from PubMed and Google Scholar. Briefly, a literature search in (1) PubMed database using keywords ((“Antioxidants" [MeSH]) AND ″4-hydroxyderricin” [Supplementary Concept]) OR “xanthoangelol” [Supplementary Concept]), resulted in n = 10; and using keywords ((“Chalcone" [MeSH]) OR ″4-hydroxyderricin” [Supplementary Concept]) OR “xanthoangelol” [Supplementary Concept]) AND “Antioxidants" [MeSH]), resulted in n = 21; and (2) the Google Scholar database using keywords *angelica keiskei* AND chalcone AND antioxidant, resulted in n = 1340. The search was limited to publications in English.

The articles obtained were further identified and screened based on the titles and abstracts related to the topic of interest, and finally 55 articles were selected to be reviewed as depicted in Fig. 1.

3. Results

Of 55 articles, 2 articles discussed the *in silico* study [21,32], 10 articles employed *in vitro* method [20,22,26,29,32–36], 6 articles used *in vivo* method [14,34,36–39], and 32 articles describe information about antioxidant activity. Studies in humans were reported in 6 articles [18,24,40–43] and of these studies, 5 articles had confirmed the efficacy of *A. keiskei* [18,24,40,42,43]. Efficacy was analyzed by measuring the decreased levels of alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), visceral fat, ghrelin, blood glucose, and increased plasma antioxidants in patients with metabolic syndrome [18,24,40,42,43]. The safety of *A. keiskei* was only mentioned by 4 articles [18,24,40,44].

In clinical studies, *A. keiskei* was administered in the form of juice, capsules, and powder [18,24,40,44] and the plant parts used were the leaves, stems, stem sap, roots, and herbs. It was reported that 5 g of *A. keiskei* herbal powder contain 2.07 mg lutein, 1.08 mg ß-carotene, 5.75 mg quercetin, and 2.57 mg catechin [43]. The stem of *A. keiskei* excretes a yellow sap rich with chalcones such as XA A-G, 4-hydroxyderricin (4-HD), isobavachalcone, xanthokeismin A-C, and xanthokeistal A [45–48]. In 100 g of dried herb granules, 198.7 mg chalcones (134.5 mg XA and 64.2 mg 4-HD) have been quantified [49]. The amount of chalcone calculated as XA in the ethanol extract of the leaves was 1.959 mg/100 g, in the ethanol extract of the stems was 2.63 mg/100 g, in the ethanol extract of the root bark was 10.51 mg/100 g, and in the root core was 1.44 mg/100 g [19,50]. The flavonoids calculated as quercetin in the aqueous

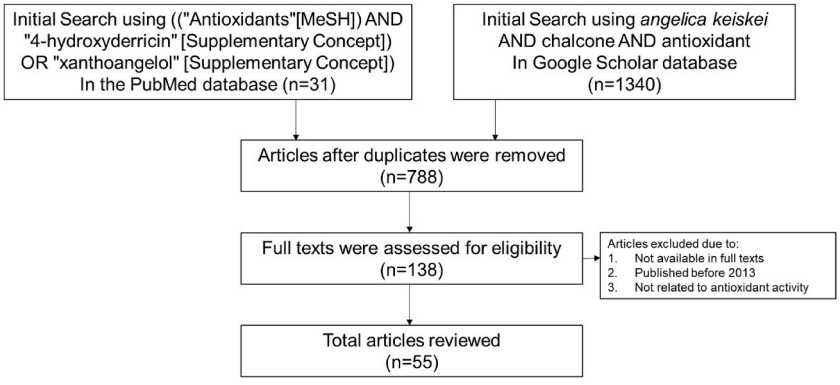

Fig. 1. The flowchart of the article search.

Table 1
The pharmacology activities *of A. keiskei* (reported using *in silico, in vitro*, and *in vivo* studies).

Pharmacology Activity	Part of Plant	*In silico*	*In vitro*	*In vivo*	Result	Ref
Nephroprotective	Stems	N/A	NAPQI-induced HEK-293 cells	N/A	Not cytotoxic and protects HEK-293 cells against NAPQI damage (IC_{50} of 2322 μg/mL)	[20]
	Leaves	N/A	NAPQI-induced HEK-293 cells	N/A	Not cytotoxic but does not protect HEK-293 cells against NAPQI damage	[20]
Hepatoprotective	Powder	N/A	Acetaminophen-induced HepG2 and HepaRG cells	N/A	Decreases apoptosis by reducing the resulting membrane permeability hepatotoxicity in HepG2 and HepaRG cells	[35]
	Leaves	N/A	N/A	carbohydrate and fat induced C57BL/6J mice (Dose: 2 g/kgBW and 4 g/kgBW for 18 weeks)	Prevent NAFLD by reducing intestinal damage, intestinal lipid absorption, and oxidative stress.	[14]
Anti-cancer	Herbs	N/A	Hep3B cells and NIH3T3 cells	N/A	Reducing cytotoxicity by preventing oxidative stress in cell cultures (IC_{50} of 15 μg/mL)	[33]
	Roots	N/A	SK-MEL-28, SK-MEL-5, and SK-MEL 31 cells	BRAF V600E/PTEN-null mice (Dose: 10 and 50 mg/kgBW)	XA and 4-HD from roots stops the cell cycle in phase G1 and apoptosis in melanoma cells.	[34]
	Roots	N/A	LM8 cells	N/A	XA and 4-HD from roots showed 32 ± 1 and 33 ± 1 % cytoxicity at 50 μM, and 54 ± 2 and 45 ± 2 % cytotoxicity at 100 μM in LM8 cells	[29]
	Roots	N/A	N/A	Male C3H/He mice Dose: 25 and 50 mg/kg BW	Inhibits tumor growth, metastases to the lungs and liver, and tumor expression associated with macrophages in animals.	[36]
Anti-obesity	Leaves and stems	N/A	N/A	Mice C57BL/6 Dose: 12.5 g/kg BW for 10 weeks	Preventing obesity and metabolic disorders through metabolic genes and the composition of the gut microbiota	[39]
Anti-diabetes mellitus	Saps	N/A	3t3-l1 cells	N/A	XA and 4-HD from saps improves glucose absorption and improves GLUT4 immunofluorescence in concentration 10 μmol/L (4HD 48 % and XA 47 %)	[26]
	Saps	DPP-IV was used as the protein target	N/A	N/A	4-HD interacts with amino acids in DPP-IV binding pocket through a single hydrogen bond with Glu206 and Phe357 (docking score of 0.17 μM).	[32]
	Saps	N/A	DPP-IV	N/A	4-HD may inhibit DPP-IV (IC_{50} of 81.44 μM)	[32]
	Sap	α-glukosidase and DPP-IV were used as the protein targets	N/A	N/A	XA interacted with amino acid residues on α-glucosidase and important residues of Glu205 and Glu206 and Phe357 in the DPP-IV binding pocket (docking score of 1.99 μM)	[21]
	Saps	N/A	α-glucosidase and DPP-IV	N/A	XA has antidiabetic activity with mechanisms to inhibit α-glucosidase and DPP-IV (IC_{50} of 10.49 μM)	[21]
Anti-inflammatory	Leaves and stems	N/A	RAW 264.7 cells	N/A	XA inhibits the production of nitric oxide (NO) and the expression of pro-inflammatory cytokines (IL-1b and IL-6) (IC_{50} of 2.7 μM)	[22]
Anti-myopati	Roots	N/A	N/A	Sprague-Dawley rats Dose: 250 and 500 mg/kg BW	Prevent muscle atrophy by reducing the mechanism of decreasing muscle protein degradation as well as activating myoblast differentiation.	[38]
Neuroprotective	Herbs	N/A	HT-22 cells	N/A	XA has a neuroprotective effect on nerve cells. Neuroprotective in Alzheimer's disease by lowering amyloid plaques.	[36]
	Herbs	N/A	N/A	Male albino mice Dose: 1, 10, 20 mg/kg BW	Has a neuroprotective effect on nerve cells. Neuroprotective in Alzheimer's disease by lowering amyloid plaques.	[36]

4-HD: 4-hydroxyderricin; DPP-IV: dipeptidyl peptidase; GLUT4: glucose transporter-4; HEK-293: human embryonic kidney-293 cells; HepaRG: human hepatic progenitor cells; Hep3B: human hepatocellular epithelial carcinoma cells; HepG2: human hepatocellular carcinoma cells; HT-22: mouse hippocampal neuronal cells; 3t3-l1: mice fibroblast cells; LM8: murine osteosarcoma cells; NAFLD: non-alcoholic fatty liver disease;

NAPQI: N-acetyl *p*-quinone imine; NIH3T3: mouse NIH/Swiss embryo fibroblast cells; RAW 264.7: macrophage-like, Abelson leukemia virus-transformed cell line derived from BALB/c mice; SK-MEL: human malignant melanoma cells; XA: Xanthoangelol.

and the methanol extract of the herbs were 12.49 mg/100 g and 22.82 mg/100 g, respectively. Moreover, the phenolics calculated as gallic acid in the aqueous and the methanol extract of the herbs were 46.67 mg/100 g and 70.49 mg/100 g, respectively [13]. The pharmacology activities *of A. keiskei* resulted from *in silico, in vitro, in vivo* studies is tabulated in Table 1, whereas the human studies are summarized in Table 2.

3.1. Nephro-hepatoprotective activity of A. keiskei

An *in vitro* study of the stem and leaves extracts of *A. keiskei* on HEK-293 cells reported a nephroprotective activity against N-acetyl-*p*-benzoquinone imine (NAPQI) induction by the stem extract, while the leaves not [20]. A study reported that chalcone revealed a strong anti-necroptosis activity (IC_{50} = 1.08 μM) and a protective activity (EC_{50} = 1.49 μM) [51].

Chalcones contained in *A. keiskei* were reported for their protective activity, in term of survival growth rate, on acetaminophen-induced human hepatoma HepG2 and HeparG cells, by increasing cell growth [35]. The administration of *A. keiskei* juice on male obese C57BL/6J mice at dose 4 g/kg BW has reduced lipid levels in the liver (12.35 mg/g) and lipoprotein lipase mRNA expression in the gastrointestinal tract [14,52]. Hepatic steatosis is the amount of intrahepatic fat at least 5 % of the weight of the liver [53].

Interestingly, a clinical study conducted on 82 alcohol drinkers aged 20–75 years, who consumed 14 or more units/week for men and 7 or more units/week for women for 1 month, had shown abnormalities in the liver function [40,54]. The intervention group was given *A. keiskei* capsules containing *A. keiskei* extract 500 mg, D-sorbitol 100 mg, and glycerin 100 mg administered twice daily between meals for 12 weeks. The intervention group showed a significant reduction of ALT and GGT [40].

3.2. Anti-cancer activity of A. keiskei

Two chalcones contained in *A. keiskei*, namely 4-HD and XA, showed a proliferative effect on the growth of fibroblast and prevented oxidative stress during cell culture. These compounds not only protect Hep3B cells but also NIH3T3 cells against oxidative stress, hence

Table 2
The efficacy safety of *A. keiskei* in humans.

Pharmacology Activity	Part of Plant or Pharmaceutical Dosage Form	Participants and Sample Size (Dose)	Result		Safety	Ref
			Baseline	After Intervention		
Hepatoprotective	Herbs	82 alcohol drinkers (Dose: 500 mg of extract twice daily for 12 weeks)	Decrease levels of ALT and GGT	↓ levels of ALT 13.4 % and GGT 6.5 %	Decrease red blood cells 1.2 % and hemoglobin 1.3 %	[40]
Anti-obesity	Capsule (Chalcurb®)	60 adults (30 men and 30 women) (Dose: capsule (Chalcurb®) 220 mg/day)	Reduces visceral fat in men 11.0 ± 0.4 cm^2 and ghrelin in both genders 525.6 ± 44.4 pg/dL.	↓ visceral fat in men 8.72 % and ghrelin in both genders 5.62 %.	No AEs	[18]
	Capsule (Chalcurb®)	15 healthy men and 26 obese adults (Dose: 220 mg capsule of the supplement 200 mg/day *A.keiskei* chalcone powder 8 % for 8 weeks)	Visceral fat 107.00 ± 43.56 cm^2, total fat 330.27 ± 59.57 cm^2, BW 73.86 ± 6.15 kg, BMI 26.92 ± 1.36, hip circumference 100.07 ± 3.2 cm.	↓ visceral fat 7.94 %, total fat 5.99 %, BW 1.1 %, BMI 1.0 %, hip circumference 0.69 %	No AEs	[24]
Anti-diabetes Mellitus	Capsules	10 adults with type II diabetes mellitus (Dose: 500 mg A.*keiskei* capsules thrice daily for 2 weeks)	Fasting blood sugar 12.6 ± 5.14 mmol/L	Did not exhibit any glucose-lowering effect.	Increase in the systolic blood pressure 10.5 %.	[41]
	Leaves and stems powder	18 adults Dose: *A.keiskei* powder in the morning and evening for 7 days.	Blood glucose 134 mg/dL until 357 mg/dL and cholesterol 233.58 mg/dL	↓ blood glucose 95.5 mg/dL until 270.8 mg/dL but does not lower cholesterol levels.	N/A	[42]
Cardiovascular	Herbs capsule	10 adults (>60 years old) 5 g capsule gelatine *A. keiskei.*	Plasma quercetin 0.0 μmol/L, plasma lutein 0.11 μmol/L, and antioxidant performance 50 % protection	↓ plasma antioxidants in metabolic syndrome such as plasma quercetin 20 %, plasma lutein 35.3 %, and antioxidant performance 20 % protection.	N/A	[43]

No AEs: No adverse events.

the cytoprotective activity of this compound is not limited to one cell type. At a concentration of 100 μM, 4-HD and XA produced cytoprotective ($p < 0.01$) by glucose oxidase induction (GOX) [33].

In this review we also report the studies of *A. keiskei* on several other cell lines, namely SK-Mel-28, SK-Mel-5, and SK-MEL-31 cells, which are human melanoma cell lines [55–57]. Melanoma is a disease in which malignant cells grow abnormally in melanocytes [58]. *In vitro* studies conducted on 4-HD and XA at doses of 5, 10, and 20 μM against SK-MEL-28, SK-MEL-5, and SK-MEL-31 cells indicated that 4-HD suppressed the proliferation of SK-MEL-31 cells significantly at a dose of 20 μM, while XA discontinued the proliferation of SK-MEL-31 cells at doses of 10 or 20 μM. In another study, 4-HD and XA subdued the growth of SK-MEL-5 and SEL-MEL-28 cells at a low dose of 5 μM [34].

The anticancer mechanism of 4-HD and XA was reported due to the arresting of BRAF/MEK/ERKs and phosphoinositide 3-kinase (PI3–K)/protein kinase-B (AKT) signaling pathways [34]. Both 4-HD and XA occupy the ATP binding site of BRAFV600E and PI3–K thus preventing the phosphorylation. Based on an *in vivo* study, 4-HD and XA at a dose of 10 mg/kg could reduce melanoma volume for about 43 and 72 % on BRAF V600E/PTEN-null mice, whereas the higher doses had decreased tumor volume for about 82 and 91 % [59]. Therefore, 4-HD and XA are predicted could attenuate the activation of BRAFV600E, PI3–K, and inhibit the phospholipase of ERK1/2 and AKT. Thus, these two chalcones may hinder tumor growth by reducing the expression of PCNA, cyclin D1, and Bcl-2 [34].

XA (10, 25, and 50 μM) prevented the production of IL-10 and MCP-1 in IL-4 and IL-13-induced macrophages M2 on highly metastatic osteosarcoma LM8 cells and human monocyte THP-1 cells [29]. 4-HD (25 and 50 μM) could inhibit the production of MCP-1 in macrophages M2, while at 50 μM it inhibits the production of IL-10 only. Osteosarcoma LM8 cells are highly metastatic in the lungs. These cell lines are used to study pulmonary metastasis and osteosarcoma [60]. THP-1 cells were isolated from the peripheral blood cells of patients suffering from leukemia [61]. THP-1 cells are used to study the function, mechanism, and pathway of anti-cancer drug candidates [62]. 4-HD and XA at concentrations of 10–50 μM could inhibit phosphorylation of the Stat3 protein [29]. *In vivo* studies indicated that 4-HD and XA (25 or 50 mg/kg BW) administered orally 2 times a day for 30 days to mice with osteosarcoma, could inhibit the tumor growth. Immunohistochemistry observations revealed that XA at a dose of 25 or 50 mg/kg could reduce the expression of F4/80, a marker of solid tumor macrophages. 4-HD and XA (25 or 50 mg/kg BW) inhibit pulmonary metastasis, suppress the increased lung weight due to tumor metastases, and inhibit liver metastase [29].

3.3. Anti-obesity activity of A. keiskei

A previous *in vivo* study disclosed the anti-obesity activity of *A. keiskei* juice. Daily dose of 12.5 g/kg BW of this plant for 10 weeks had reduced the body weight by 17.3 % [39] due to alteration in metabolic gene expression and the composition of the gut microbiota [24,39]. The chalcones of *A. keiskei* were predicted to play role in these activities [39].

Patients ($n = 60$) with metabolic syndrome and obesity who were given *A. keiskei* (Chalcurb®) 220 mg/capsule once a day with dinner for 12 weeks, demonstrated a reduction of BW on the 84th day although not significant compared to that of the placebo group ($p = 0.069$) in both females and males. Male participants in the intervention group experienced a significant decrease in ghrelin compared to the placebo group, and reduced levels of ghrelin were thought to correlate with reduced food intake during the study [18]. Visceral fat was measured on days 14, 56, and 84. Ghrelin is considered a hormone that controls hunger. The intervention group experienced a significant decrease in ghrelin compared to the placebo group, and reduced levels of ghrelin were thought to correlate with reduced food intake during the study [18].

Another clinical study in 26 obese adults (BMI of 25–30), age 40–65 years, and a waist circumference of >85 cm treated with *A. keiskei* chalcone powder dose of 200 mg/day for 8 weeks, indicated a significant visceral fat area (VFA) loss by 7.94 % ($p < 0.05$), a reduction of total amount of fat (TFA) by 5.99 % ($p < 0.05$), and weight loss ($p < 0.01$) in the intervention group compared to the control group (15 healthy men) at the end of the study. No adverse events (AEs) was observed until week-8, thus confirmed the safety of this drug [24].

A clinical study towards 9 adults (30–65 years) with metabolic syndrome treated with 6.2 g/day (at breakfast and dinner) of *A. keiskei* leaves and stems powder for 8 weeks resulted in the significant decrease of the VFA and TFA at week-8 compared to week-0 ($p < 0.01$). Moreover, the participants' BW and BMI also reduced ($p < 0.05$) [49]. Treatment with *A. keiskei* (Chalcurb®) 220 mg/capsule revealed no significant effect in total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and overall glucose levels (fasting glucose and HBA1c) [18].

Similarly, another study reported that *A. keiskei* may prevent metabolic syndrome by reducing visceral fat. LDL cholesterol levels at week-4 and week-8 were lower than in week-0 ($p = 0.090$ and $p = 0.086$, respectively). The chalcones of *A. keiskei* were predicted could inhibit β-hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase [24].

3.4. Anti-diabetes mellitus activity of A. keiskei

A previous *in silico* study of XA isolated from the yellow sap of *A. keiskei* reported that this chalcone interacts with Glu205 and Glu206 in α-glucosidase and with Phe357 in DPP-IV similarly to that of known inhibitors of the enzymes [21] Moreover, *in vitro* study disclosed that the other chalcone, 4-HD, inhibits DPP-IV (IC_{50} of 81.44 μM). 4-HD could attach to the DPP-IV with similar binding mode to sitagliptin, an inhibitor of DPP-IV [32]. 4-HD and XA were reported could increase glucose absorption in 3T3-L1 cells by 8 % and 47 %, respectively. At a dose of 20 μmol/L, 4-HD and XA showed an increase in glucose transporter-4 (GLUT4) through immunofluorescence [26].

A clinical trial study on female patients with type 2 diabetes (T2DM) (18–59 years) treated with 500 mg A. *keiskei* capsules thrice daily (1.5 g/day) for two weeks as an add-on therapy, resulted in no glucose reduction effect. In monitoring the AEs, there was a

significant increase in systolic pressure ($p = 0.014$) on the intervention group, but not in the placebo group [41].

Another report of patients with hyperglycemic (blood glucose 130–169 mg/dL) and hypercholesterolemic (200–239 mg/dL) aged 30–70 years, the treatment with *A. keiskei* powder twice per day for 7 days indicated an increase of the average cholesterol and a decrease in the average fasting glucose levels [42].

3.5. The effect of A. keiskei on cardiovascular

A clinical study on 10 adults (>60 years) with metabolic syndrome administered with 5 g of *A. keiskei* powder in capsules once a day, resulted in a significant increase of total plasma values of antioxidants at 60 and 180 min about 44 and 47 % ($p < 0.05$), but the level of these antioxidants decreased slightly after lunch, and increased again at 360 and 420 min ($p < 0.05$) [43].

In vitro study revealed that 4-HD and XA effectively inhibit platelet aggregation at a dose of 42.3 μM (IC_{50} of 46.1 μM) [28]. Platelet aggregation is formed due to the presence of atherosclerotic plaques resulting in ischemic tissue injury and organ dysfunction [63].

3.6. Anti-inflammatory activity of A. keiskei

The effect of leaves and stem extracts of *A. keiskei* 10 μg/mL in lipopolysaccharide-induced RAW 264.7 cells revealed an inhibition of nitric oxide (NO) production and IL-1B and IL-6 expression [22]. In addition, isobavachalcone of *A. keiskei* also inhibits the expression of nitric oxide synthase (iNOS) in macrophages-induced toll-like receptors (TLR) [64].

3.7. Anti-myopathy activity of A. keiskei

Oral administration of *A. keiskei* in dexamethasone-induced rats reduced muscle atrophy damage through mitogen activated protein kinase (MAPK) at a dose of 500 mg/kg. *In vitro* study performed on colon cancer cells induced by dexamethasone 20 μM showed that 4-HD dose of 100 μM protected the myosin heavy chain (MHC) degradation through suppressing the expressions of MAFbx, MuRF-1, and myostatin [38].

3.8. Neuroprotective activity of A. keiskei

The neuroprotective effect of XA on HT-22 cells against oxidative stress resulted that at a dose of 40 μM, XA increased GSH and SOD [36]. HT-22 are cell lines derived from hippocampal nerve cultures of mice and used for *in vitro* testing in neurodegenerative [36].

Furthermore, XA at a dose of 20 mg/kgBW in scopolamine induced-mice can improve the symptoms of Alzheimer's disease. XA showed significant results ($p < 0.001$) of memory improvement observed in the Y-maze test and reduced beta amyloid ($p < 0.001$) [36].

4. Discussion

The antioxidant activity of chalcones is thought due to the presence of free hydroxyl groups and the α,β-double bond (Fig. 2). Chalcones exhibit antioxidant activity either directly or indirectly [65,66]. Chalcones prevent oxidative stress by lessening the production of ROS, RNS, and superoxide [67]. The ethanol extract of *A. keiskei* leaves has shown antioxidant activity with an IC_{50} value of 7.73 μg/mL [68]. The chalcone content in this plant plays a role in scavenging the free radical of 1,1-diphenyl-2-picrylhydrazyl (DPPH)

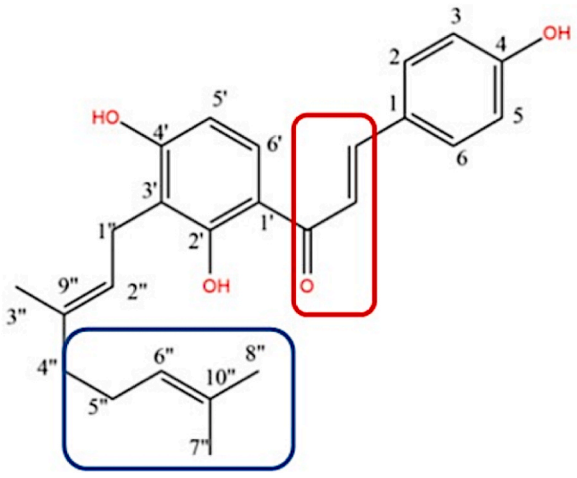

Fig. 2. 2D Structure of the Xanthoangelol (blue box indicates the prenyl group, red box indicates the α, β-double bond). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

by donating the hydrogen of the hydroxyl group, and chalcones act as substrates for free radicals such as superoxide and hydroxide [69]. Antioxidants exert their activity by transferring their hydrogen to DPPH molecule which possesses a lonely radical electron [70]. When the free radical of DPPH molecule is combined with the single electron of the hydrogen of an antioxidant, the purple color of DPPH shifts to yellow [71].

Nephrotoxicity is marked by an abnormal elevation of blood urea nitrogen (BUN) and serum creatinine (sCr), along with a decrease in glomerular filtration rate (GFR) [36,72,73]. Drug-induced nephrotoxicity mechanisms include tubular cells damage, glomerular hemodynamic changes, crystal nephropathy, thrombotic microangiopathy, and inflammation [70,74]. Nephrotoxicity may lead to acute kidney injury (AKI). AKI occurs when there is an imbalance between oxygen and nutrients induced by impaired circulation to the nephron and increased energy needs due to oxidative stress [75]. Nephrotoxicity can be initiated by exposure to chemical compounds and drugs such as cadmium, mercury, arsenic, lead, glycolic acid, and ethylene glycol [76,77], whereas drugs triggering kidney damage include cisplatin, angiotensin-converting enzyme (ACE) inhibitors, aminoglycosides, non-steroid anti-inflammatory drugs (NSAIDs), and acetaminophen [78–82].

Acetaminophen is an antipyretic-analgesic drug that is widely used because it does not inhibit the catalytic work of COX-1 in the stomach, thus the production of prostaglandin is not altered [83]. However, acetaminophen is biotransformed via the oxidative reaction of cytochrome P450 to its toxic metabolite namely NAPQI by CYP2E1 and CYP2A6 [84], and its long term use may initiate nephrotoxicity due to the depletion of glutathione in the liver [85,86]. When excessive NAPQI metabolite enters the mitochondria, it induces oxidative stress, mitochondrial dysfunction, and necrotic cell death [87,88].

Chalcones have been reported for their pro-inflammatory activity by reducing the expression of inflammatory cytokines, lowering ROS levels, preventing mitochondrial damage and cell apoptosis via the inhibition of mitogen-activated protein kinase (MAPK) pathway, inhibition of nuclear factor-kappaB (NF-κB), and activation nuclear factor-erythroid-2 related factor 2 (Nrf2) [85]. Chalcones has shown their nephroprotective activity against cisplatin-induced kidney cells, by blocking MAPK signaling [89].

Chalcones have conveyed their necroptosis signaling blockade activity, which is the main mechanism for the occurrence of the kidney proximal tubule cell injury [51]. Chalcones can inhibit the expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-1β, IL-6, and miR-146a [90]. Mechanism of chalcone as nephroprotector in kidney toxicity induced by NAPQI

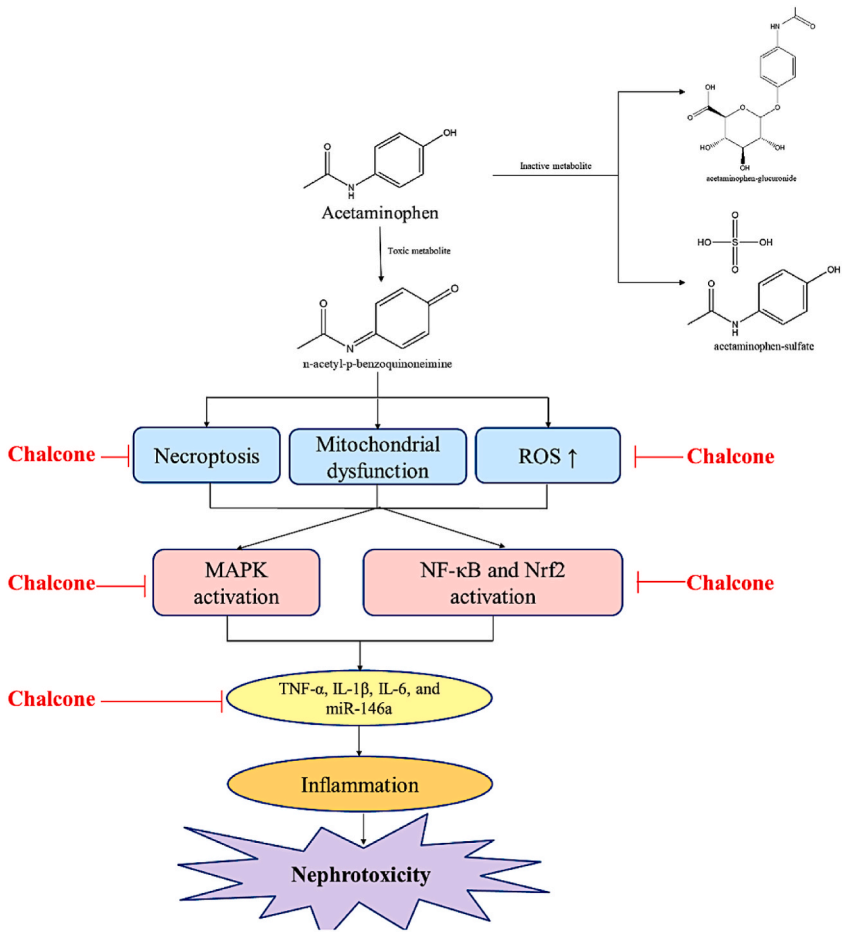

Fig. 3. Mechanism of chalcone as nephroprotector in kidney toxicity induced by NAPQI. Adapted and modified from Refs. [75,91,92].

Fig. 3.

Hepatoxicity occurs due to cell death due to oxidative stress and drugs [93,94]. ROS is pathophysiologic for acute liver injury, produced in the mitochondria and endoplasmic reticulum of hepatocytes through the cytochrome P450 enzyme [95]. When there is an excessive of ROS production, an increase serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) will eventually occur [96,97]. A long-term consumption of alcohol may lead to hepatoxicity [98]. Moreover, certain medications, e.g., paracetamol, sodium diclofenac, diethyldithiocarbamate, ketoconazole, and anti-tuberculosis, may also initiate liver damage [94, 99–101].

HepG2 and HepaRG cells are human hepatoma cell lines [102]. HepG2 cells were used in studies of the metabolism and hepatotoxicity of drugs [103]. HepaRG cells exhibit the activity of the cytochrome enzyme [102]. HepaRG cells are used for biological interpretation of the effects of chemical exposure on the liver [104]. GGT is a hepatocyte plasma membrane enzyme that plays a role in the antioxidant mechanism by catalyzing gamma-glutamyl glutathione to the acceptor peptide [40,105,106].

Hep3B cell is derived from hepatocellular carcinoma cell lines and NIH3T3 cell line was derived from mouse embryonic fibroblasts and progressed until pre-birth [107,108]. Hep3B cells and NIH3T3 cells were used in in vitro anti-cancer assays [109,110]. GOX catalyzes glucose oxidation in the presence of oxygen for the production of gluconic acid, resulting in oxidative damage to cells [111, 112].

Cancer is an uncontrolled and multistage change in mutants and cell proliferation [113]. ROS can influence the occurrence of cancer by stimulating tumorigenesis, and cell transformation/proliferation, to cause cell death [114]. Compounds used to reduce ROS-induced cell mutation and delay the initiation of cancer are commonly called antioxidants [115]. Chalcones have been known for their antioxidant activity [116].

Obesity is the accumulation of excessive fat in the body [117]. Obesity is characterized by chronic inflammation that causes a permanent increase in oxidative stress [118]. In the body, an increase in ROS and fat accumulation can lead to obesity and result in metabolic syndrome [117]. Foods rich in oxidants can be used to prevent an increase in oxidative stress to overcome obesity [119]. The juice is made from fresh vegetables in the form herbs of *A. keiskei*. In addition, fasting blood glucose insulin, and serum lipid levels are significantly reduced [39].

4-HD isolated from stem sap *A. keiskei* has been reported for its antidiabetic activity with a mechanism of inhibiting DPP-IV, wherein 4-HD interacts with Glu 206 and Phe357 [32]. Thus 4-HD and XA may increase glucose uptake by increasing GLUT4 through the signaling pathway of liver kinase B1 (LKB1)/adenosine monophosphate-activated protein kinase (AMPK) in adipocyte 3T3-L1 [26]. It was announced that *A. keiskei* powder is effective in lowering blood glucose levels, but not effective in lowering blood cholesterol levels [42].

Excess glucose metabolites will cause damage to ß-pancreatic cells and result in diabetes mellitus [120]. Oxidative stress causes an imbalance in the production of free radicals and antioxidant systems resulting in a decrease in insulin sensitivity [121,122]. ROS production will lead to the breakdown of insulin and increased apoptosis [120]. The main chalcones of 4-HD and XA extracted from the roots of *A. keiskei* have antiplatelet [28,123]. In the presence of compounds that enhance endothelial function and inhibit platelet aggregation, it will reduce the formation of platelet aggregation [124].

Chalcones have an inflammatory response by inhibiting the secretion of tumor necrosis factor-alpha (TNF-α) and the expression of nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) induced lipopolysaccharides [125]. Chalcone derivative compounds have antioxidant properties by preventing structural damage in acute LPS-induced lung injury [126]. Myopathy is muscle weakness without sensory loss [37]. Drug induced myopathy include statin, proton pump inhibitor, gabapentin, and dexamethasone [127–130].

5. Conclusions

Chalcones have been reported to exhibit direct and indirect antioxidant activity and prevent oxidative stress by decreasing ROS, RNS, and superoxide production. In this paper, we summarized the parts of *Angelica keiskei* Koidzumi, a plant that contains chalcones, for their pharmacological activities to combat diseases triggered by oxidative stress such as kidney disease, liver injury, obesity, diabetes mellitus, cardiovascular disease, inflammation, myopathy, and neurotoxicity damage. Chalcones in *A. keiskei* have been extensively studied by *in silico, in vitro, in vivo*, and its efficacy to humans and had proven their activity in preventing several diseases caused by oxidative stress, including nephroprotective, hepatoprotective, anti-cancer, anti-obesity, anti-diabetic, cardiovascular, anti-inflammatory, anti-myopathy, and neuroprotective. Most studies concerned on the anti-obesity activity due to the capability of this plant in decreasing visceral fat, ghrelin, total fat, body weight, body mass index, and hip circumference. Efficacy of *A. keiskei* was confirmed in anti-obesity, hepatoprotective, anti-diabetes mellitus, and increasing plasma antioxidants in patients with metabolic syndrome. *A keiskei* is safe as proven by only mild or no adverse events reported, thus it is prospective to be further developed for a safe antioxidant nutraceutical.

Funding

The authors thank the Rector of Universitas Padjadjaran via the Directorate of Research and Community Engagement for facilitating this study and funding the article processing charge (ALG Grant No. 1549/UN6.3.1/PT.00/2023 to Prof. Jutti Levita)

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

Data availability statement

The data generated in the present study may be requested from the first author upon reasonable request.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Ika Wahyuni: Writing – original draft, Formal analysis, Investigation, Data curation. **Diah Lia Aulifa:** Supervision, Writing – review & editing, Data curation, Project administration. **Aziiz Mardanarian Rosdianto:** Data curation, Project administration, Supervision, Writing – review & editing. **Jutti Levita:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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