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A review of traditional uses, phytochemistry and pharmacology of *Portulaca oleracea* L.

Milad Iranshahy[a], Behjat Javadi[b], Mehrdad Iranshahi[a], Seyedeh Pardis Jahanbakhsh[c], Saman Mahyari[c], Faezeh Vahdati Hassani[d], Gholamreza Karimi[d*]

[a]*Biotechnology Research Center and School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*

[b]*Department of Traditional Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*

[c]*Pharmaceutical Research Center, Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*

[d]*Pharmaceutical Research Center, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*

[*]Correspondence to: Pharmaceutical Research Center, Pharmacy School, Mashhad University of Medical Sciences, Mashhad, Iran, P.O. Box 91775-1365, Mashhad, Iran. KarimiG@mums.ac.ir

Abstract

Ethnopharmacological relevance

Portulaca oleracea L. is a widespread medicinal plant that is used not only as an edible plant, but also as a traditional medicine for alleviating a wide spectrum of diseases. It is a well-known plant in the European Traditional Medicine. PA is mentioned by *Dioscorides* (40–90 CE), with the name of "andrachne".

Aim of the review

In this study, we provide detailed information on botany, traditional uses, phytochemistry, pharmacological uses, pharmacokinetics and safety of *P. oleracea*.

Materials and methods

An extensive search on electronic databases including PubMed, Web of Science, Google Scholar, ScienceDirect, Scopus, conference papers, local herbal encyclopedias, articles,

books (in English, French, Arabic, Persian, *etc*.) and also a number of unpublished handwritten manuscripts was done to find articles have been published between 1956 and 2015 on pharmacology and phytochemistry of *P. oleracea.*

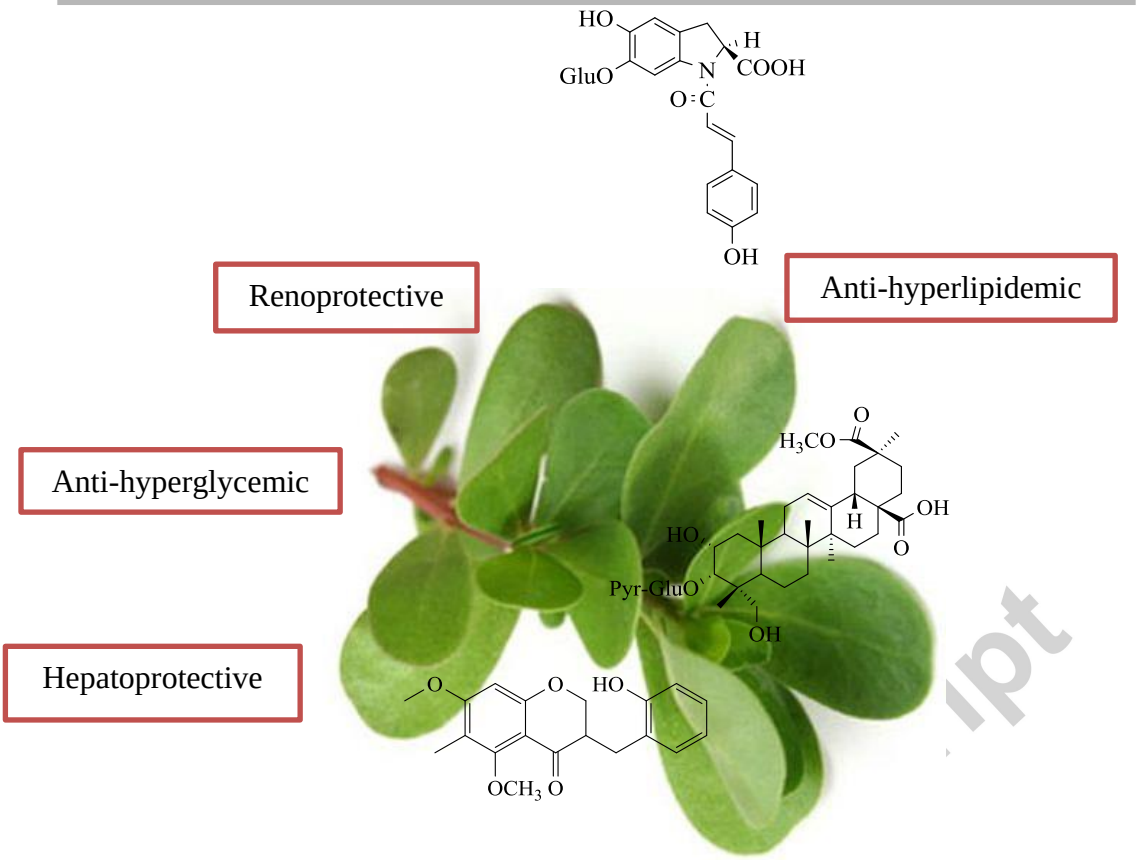
Results

P. oleracea has been addressed in *De Materia Medica* as an astringent, and a remedy for headaches, inflammation of the eyes and other organs, burning of the stomach, erysipela, disorders of the bladder, numbness of the teeth, excessive sexual desire, burning fevers, worms, dysentery, hemorrhoids, eruptions of blood, and bites. Phytochemical investigations revealed that this plant a wide range of secondary metabolites including alkaloids, terpenoids, flavonoids and organic acids. The most important pharmacological activities are renoprotective activities and effects on metabolism. *P. oleracea* could successfully decrease blood glucose and lipid profile of patients with metabolic syndrome. The safety of *P. oleracea* has been reported in many clinical trials.

Conclusion

Modern pharmacological studies have now proven many traditional uses of *P. oleracea*, including anti-hyperglycemic and anti-hyperlipidemic, renoprotective and hepatoprotective effects. In addition, in many clinical trials *P. oleracea* showed no adverse effects and constipation was reported as the most frequent adverse effect.

Graphical abstract



Keywords: *Portulaca oleracea* L., Ethnopharmacology, Anti-hyperlipidemic, Anti-hyperglycemic, Hepatoprotective, Renoprotective

1. Introduction

Portulaca oleracea L. (PA) is an annual herbaceous plant with reddish stems and alternate leaves from family Portulacaceae. PA is distributed in many parts of the world and specifically the tropical and subtropical areas (Zhou et al., 2015). In many countries, PA has been extensively used as a potherb with green or yellow leaved forms (Karimi et al., 2004).

PA has been used as a traditional medicine for alleviating a wide spectrum of diseases including gastrointestinal diseases, respiratory problems, liver inflammation, kidneys and bladder ulcers, fevers, insomnia, severe inflammations, headaches, *etc* (Razi, 1968; Ibn Sina, 1987). Dioscorides (40–90 CE), the father of pharmacology, has mentioned medicinal properties of this plant in his pharmacology book *De Materia Medica* (Osbaldeston, 2000). Since then, medicinal properties of PA were mentioned in many other landmark medical textbooks such as *Canon of Medicine* by Avicenna, *Zakhireh Kharazmshahi* by Jorjani, *Al-Hawi* by Rhazes and other Traditional Persian Medicine (TPM) books. PA is also listed in a number of pharmacopoeias including Pharmacopoeia of PR China (Chinese Pharmacopoeia Commission, 2010) and The Ayurvedic Pharmacopoeia of India (Anonymous, 1989). Modern pharmacological studies revealed that PA has several biological activities such as antioxidant (Karimi et al., 2011), antimicrobial (Dan, 2006), bronchodilator (Malek et al., 2004) renoprotective (Hozayen et al., 2011), neuroprotective (Wang et al., 2007), muscle relaxant (Parry et al., 1993), hepatoprotective (Eidi et al., 2015), antiulcerogenic (Kumar et al., 2010), and anti-fertility effects (Hanumantappa et al., 2014). In addition, phytochemical investigations have demonstrated the presence of flavonoid, alkaloid, terpenoid, organic acid, Fatty acids, minerals, and vitamins in this plant (Petropoulos et al., 2016, Zhou et al., 2015).

In this paper, we prepared an update review of botany, phytochemistry, pharmacology, safety and clinical applications of PA with an especial focus on its widespread uses in different traditional medicine systems around the word. Hopefully, this information is helpful in designing future animal and clinical studies and in developing new pharmaceuticals containing PA or its active ingredients.

2. Botany

Portulaca oleracea L. commonly known as Purslane is a herbaceous weed belonging to family Portulacaceae. The name *Portulaca* means milk, which is derived from the Latin name 'laca", because the plant contains a milky juice (Boulos et al., 1984). *P. oleracea* has been recorded generally in the French, Spanish, Mexican, and Venezuelan Pharmacopeias (Dweck, 2001). It is grown in all warm countries like India. It can grow in almost any region including flower beds, lights area, corn fields, and waste places. It is also found in the temperate countries of Europe, Canada, America, Australia and New Zealand (Masoodi et al., 2011). The plant is an annual succulent herb which has thick fleshy leaves adapted to storing water which are sub-sessile, 6.25 mm long, alternate or sub-opposite; Stems 15.30 cm long, mostly glabrous, reddish and swollen at the nodes; Flowers few together, in sessile terminal heads. Microscopic analysis of the powder from the leaves shows sieve plates, spherical mineral crystals, vessels with bordered pits and tracheid with spiral, annular and scalariform thickening (Banerjee and Mukherjee, 2003).

3. Ethnobotany and Traditional knowledge

PA is a widespread medicinal plant that is used not only as an edible plant, but also as a traditional medicine for alleviating a wide spectrum of diseases. It is a well-known plant in the European Traditional Medicine. PA is mentioned by *Dioscorides* (40–90 CE), with the name of 'andrachne'. He addressed the plant in his *De Materia Medica* as an astringent, and a remedy for headaches, inflammation of the eyes and other organs, burning of the stomach,

erysipelas, disorders of the bladder, numbness of the teeth, excessive sexual desire, burning fevers, worms, dysentery, hemorrhoids, eruptions of blood, and bites of the seps. He also believed that PA is beneficial in the treatment of bowels troubled with excessive discharges and pustules of the head (Osbaldeston, 2000). *Galen* in his book, *On the Properties of Foodstuffs*' states: "As for its non-irritating viscidity, purslane cures inflammation of the gum" (Powell and Wilkins, 2003). Pliny (23-79 AD), mentioned PA with the name of 'porcilaca' and considered it as a *veritable panacea* in his encyclopedic work, *Naturalis Historia* (Bosi et al., 2009). Evelyn (1620 –1706), English writer and gardener, in his book *Acetaria, a discourse of Sallets* has mentioned this plant as 'Purslain' and 'Portulaca' and described it as a moist and cooling, appetite enhancer and thirst-quenching plant which is very profitable for hot and bilious tempers, as well as sanguine (Evelyn, 1699).

In Italy, PA has been used to treat a variety of diseases such as head, stomach intestine and kidney pains, intestinal worms, dysentery, urogenital infections, urinary inflammations, scurvy, fever, hemorrhoids, hemoptysis, mouth and gum ulcers, toothaches, reddened gums, skin rashes, pimples and eye inflammations, raspy voice, lizard bites and as a diuretic and anaphrodisiac medicine (Bosi et al., 2009; Iserin et al., 2001). A poultice of PA leaves is also applied to alleviate headaches, gastric acid, eye inflammations and to prevent gangrene (Iserin et al., 2001). Moreover, its leaves are taken as a salad singly or mixed with *Allium ampeloprasum* and *Urtica sp*. to induce diuresis (Guarrera and Savo, 2013). In Central Italy (Marche, Abruzzo and Latium), PA reputed to have refreshing, detoxifying, emollient and antiscorbutic properties and is added to salads (Guarrera, 2003). In Southern Italy, (Peninsula Sorrentina) it is believed to have strong diuretic effects and a mild laxative action (De Feo, 1992). In Eastern Mallorca (Balearic Islands, Mediterranean Sea), PA aerial part is orally used to regulate blood pressure (Carrio and Valles, 2012). In Greece, PA is eaten as salad, and cooked or baked in pies, soups and omelets or cooked with poultry. During the winter

months, dried PA is used as a tea for sore throat and earache. PA is consumed during pregnancy and lactation and is recommended for patients with diabetes (Simopoulos, 2004; Brussell, 2004). PA is also used to cure inflammations of the urinary system and high cholesterol level (Megaloudi, 2005; Albala, 2011). According to Abulcasis (Al-Zahrawi, Arab-Andalusian physician (936–1013)), PA seeds were orally administered to cure respiratory problems, cough, anorexia, spermatorrhea and hot fevers in Spain. PA aerial parts were also used for the treatment of cough, intestinal ulcers, polyuria and infertility caused by excessive heat. The seeds were externally applied for aphtha, anosmia and hoarseness while the aerial parts were applied to alleviate headache, meningitis, epistaxis, aphasia, gout and arthralgia (Al-Zahrawi, 2004).

In Albania, PA and its juice are used as an anti-rheumatic medicine (Pieroni et al., 2005). In Cyprus, PA is freshly consumed as a salad and used for alleviating mental disorders, CNS and cardiovascular diseases (Della et al., 2006; Gonzalez-Tejero et al., 2008). In Albania and Cyprus, it is also used as a common nutritional source and to treat musculoskeletal disorders (Gonzalez-Tejero et al., 2008).

In Africa, PA has many traditional uses such as curing hypercholesterolemia, shortness of breath, gastric problems, abdominal complaints, diabetes, worms, hypertension, obsession, madness, intestinal ulcers, sinusitis, spastic paralysis, leprosy, earache, toothache, urticaria, anthrax, boils and abscesses (al-Nafis, 1999; Habtemariam et al., 1993; Lans, 2006; Samuelsson et al., 1993). In Morocco, PA shoots are steamed and mixed with green olives, garlic, olive oil and spices to prepare a salad (Tanji and Nassif, 1995; Benkhnigue et al., 2010). PA also is used as an energizing food and gastric tonic commonly in combination with the leaves of *Malva sylvestris* L. (Bachar et al., 2016). In Benin (West Africa), PA leaves are used to cure leprosy (Bello et al., 2013). PA is consumed raw and also masticated to induce salivation in North Cameroon (Malzy, 1954a; Malzy, 1954b). In Ivory Coast, grinded PA

twigs and leaves are used to facilitate childbirth (Béné et al., 2016). In Somalia, PA whole plant is used orally and topically to cure abdominal complaints, dysmenorrhea, intestinal wounds, sinusitis, spastic paralysis and leprosy (Samuelsson et al., 1993). In Nigeria, it is eaten for the treatment of muscular pains (Parry et al., 1993).

In traditional Chinese medicine PA is known as “vegetable for long life” (Chen, J. et al., 2003) and is used orally for the treatment of dysentery with bloody stools, and externally for swellings, abnormal uterine bleeding, hemorrhoid bleeding, sores, erysipelas, eczema, snake- and insect-bite (Chen et al., 2009). In Nepal (Kali Gandaki watershed area), PA leaves juice is used as a drink. Moreover, PA leaves and seeds are administered for blood purification and to cure cardiovascular complaints and circulatory diseases and dental problems. A paste made of the fruits and seeds of PA are applied on the teeth and gum to cure toothache (Joshi and Joshi, 2000). In Philippines aerial parts of PA are recommended as a wound healer, mild diuretic, anti-scorbutic, refrigerant and anti-rheumatic (Belcheff, 2012).

This plant is normally used as a vegetable to prepare curry in India (Anusha et al., 2011). Moreover, it is used in Ayurvedic medicine to cure diseases of the lungs, liver, kidneys, bladder and bowels, scurvy, asthma, leprosy, hemorrhoids, spitting of the blood and gastric inflammation (Belcheff, 2012; Nadkarni KM 1996). The juice of the plant is also used to treat burning sensation. Plant and the seeds are used in diseases of kidney, bladder and lung. It is used externally to alleviate burns, scalds and skin diseases (Belcheff, 2012).

There is convincing evidence suggesting the presence of PA in the New World in pre-Columbian period (Chapman et al., 1973; Byrne and McAndrews, 1975). PA has been used by aboriginal Americans and Australians as "greens" and a medicinal plant (Chapman et al., 1973; Liu et al., 2000). In America, PA aerial parts are used to cure cold, gout, headache, stomachache, excessive menstrual flow and cough. Moreover the leaves juice is

recommended to alleviate inflammation of the male genitalia (Belcheff, 2012). In Dominica, West Indies, PA is used for the treatments of intestinal worms (Quinlan et al., 2003). In Trinidad and Tobago PA is consumed as a cooling, analgesic and gastroprotective drug and to cure urinary problems, high cholesterol levels and shortness of breath (Lans, 2006). In Columbia, PA is applied externally as an emollient, and to cure tumors and callosities (Belcheff, 2012).

In Australia, PA aerial parts are eaten to cure scurvy, irritations and inflammations and as a diuretic and antibiotic (Belcheff, 2012).

PA has been long used as a common food item and a medicinal plant in the Central Asian and Middle Eastern countries. In Pakistan, fresh aerial parts of PA, have long been considered valuable in the treatment of urinary and digestive problems. The diuretic properties of the juice make it useful in the treatment of bladder ailments such as dysuria. The plant is also used as a remedy for gastrointestinal problems such as diarrhea and dysentery. PA Seeds are reputed to be demulcent, diuretic and vermifuge (Ullah et al., 2013).). Fresh leaves are slightly warmed and applied topically on swelling joints. The extract of stem is applied on skin to cure burning sensation. PA is believed to be depurative, febrifuge, cardiac stimulant and used in the treatment of coughs, earache, skin infections, sores and burns (Abbasi et al., 2015). In Afghanistan, PA seeds are used as an antidiarrheal and for throat infection (Younos et al., 1987).

In United Arab Emirates (UAE) and Oman, PA aerial parts are considered as a useful febrifuge (El-Ghonemy, 1993). In Jordan, PA seeds are used as a blood purifier and an aphrodisiac (Lev and Amar, 2002). In Sivrice region, turkey, PA leaves are used as a nutrient food item and to cure diarrhea, diabetes, headache, ulcers, urinary disorders and wounds. It is recommended to drink one cup of PA leaves decoction on an empty stomach in the morning

(Cakilcioglu and Turkoglu, 2010). In Saudi Arabia, PA is traditionally consumed for the treatment of liver and gastrointestinal problems, and inflammatory diseases (Al-Asmari, 2014).

In Persia, PA is known as 'Khorfeh' and its leaves and seeds are widely used in cooking and confectionary. PA is also an important medicinal plant in the Traditional Persian Medicine (TPM). In his *Canon of Medicine*, Avicenna (981–1037), a well-known Iranian philosopher and physician, recommended this plant as a medication for severe inflammations, erysipelas, pulsatile headaches caused by hot temperament, eye pain, hemoptysis, gastritis, liver inflammation, and intestinal ulcers. He used PA for the treatment of kidneys and bladder pains and ulcers (Ibn Sina, 1987). Jorjani (1042–1136), another eminent TPM scholar, used PA to treat a broad array of diseases including hemorrhagic vomiting, fevers, insomnia, blepharitis, mouth ulcers, cough, tonsillitis and asphyxia and nocturnal emissions. He also believed that PA is an effective remedy for heart weakness and palpitation (Jorjani, 1976). Moreover, this plant has been reported to be a gastrointestinal tonic, anti-appetite, anaphrodisiac, burn healer and antihemorrhoid (Aqili Khorasani, 1992). Rhazes (854-925) distinguished Persian physician, recommended chewing PA leaves for the treatment of teeth sensitivity. He also used the plant externally to cure warts, aphtha and bleeding (Razi, 1968). In Mashhad, the capital of Razavi Khorasan Province, Iran, PA seeds and leaves are consumed as an antitussive, febrifuge, anti-thirst, food digestive, depurative, anti-hemorrhoids and diuretic medicine (Amiri and Joharchi, 2013). In Ilam Province of Iran, all parts of PA are used as an anti-parasite (Ghasemi Pirbalouti et al., 2013). In Kohghiluyeh va Boyer Ahmad province of Iran, aerial parts of PA are eaten as a stomach tonic (Mosaddegh et al., 2012). According to the main TPM pharmacopoeias, 80 g of the extract of the fresh leaves and 20 g of the dry seeds of the plant are applied in simple preparations (Aqili Khorasani, 2007).

In TPM, PA is mainly used in compound preparations in order to enhance its therapeutic effects as a result of synergistic effects with other plants. Fresh aerial parts of PA and its juice are mainly used in compound preparations. Moreover, the ‘seed's milk’ which is prepared by macerating seeds powder in hot water and subsequently filtering it, is another common preparation of this plant (Aqili Khorasani, 1992). The ‘seed's milk’ is used as a brain and heart refrigerant, and to treat headaches, meningitis, encephalitis, thirst, melancholia, conjunctivitis, epistaxis, mouth ulcers, suffocation, tonsillitis, pleurisy, palpitation caused by excessive heat of the heart, *etc* (Chashti, 1884).

The most frequent traditional uses of PA in various countries seems to be treatment of headache, inflammations, teeth problems, stomach illnesses, respiratory diseases, worms, fever, scurvy and epistaxis, wounds and ulcers.

Table 1 provides a summary of the traditional uses of PA in different cultures.

4. Phytochemistry

Purslane presents a variable chemical constituents mainly belong to flavonoid (Yan et al., 2012), alkaloid (Xiang et al., 2005), terpenoid (Sakai et al., 1996) and organic acid (Xin, H.-L. et al., 2008) and other classes of natural compounds including terpenoids, fatty acids, polysaccharides, vitamins, sterols, proteins, and minerals. In addition to the various environmental factors, culture conditions and harvesting time, different extraction solvents can influence the final content of bioactive compounds. Among different extraction methods, the methanol extraction and chloroform-methanol mixture revealed to be the most efficient and reliable method to obtain the highest content in total phenolic compounds and the maximum yield in saturated and mono-unsaturated fatty acids (Petropoulos et al., 2016).

4.1. Flavonoids

Flavonoids are one of the main active ingredients of purslane. The concentrations of flavonoids vary in the different plant parts. The highest amount is found in the root followed by stem and the leaf. Kaempferol, apigenin, luteolin, myricetin, and quercetin are major flavonoids in PA (Zhu et al., 2010). Portulacanones A-D (figure 1 compounds 9-12) are homoisofalvonoids with unique chemical structure have been isolated from aerial parts of PA (Xu et al., 2006). The flavonoids in PA are the biologically active constituents. The total flavonoid and phenolic contents and antioxidant activities of PA were measured in the dichloromethane, ethyl acetate, n-hexane, and methanol extracts (Salehi et al., 2013). A strong correlation between antioxidant activity and the total phenolic and flavonoid content of the methanol extract of PA was observed (Salehi et al., 2013).

4.2. Alkaloids

Another important chemicals have been identified in PA are different types of alkaloids. Alkaloids including N-trans-feruloyltyramine, dopa, dopamine, and a high concentration of noradrenaline are found in PA (Petropoulos et al., 2016). The contents of alkaloids dopamine and noradrenaline are different in the stem, leaves (highest concentration observed), and seeds of PA. Furthermore, the extraction procedure with distilled water gives the highest content of noradrenaline, while the methanol extraction provides the highest content of dopamine (Yue et al., 2005). Oleracein A-E (figure 1 compounds 1-5), and (3R)-3,5-bis(3-methoxy-4-hydroxyphenyl)-2,3-dihydro-2(1H)-pyridinone and 1,5-dimethyl-6-phenyl-1,2-dihydro-1,2,4-triazin-3(2H)-one (figure 1 compounds 6, 7) are new alkaloids, isolated from this plant (Tian et al., 2014 and Xiang et al., 2005). Antioxidant activities of the phenolic alkaloids oleracein A, oleracein E and oleracein B from PA were determined, based on inhibitory effect on hydrogen peroxide-induced lipid peroxidation and scavenging activity against 1,1-diphenyl- 2-picryl-hydrazyl (DPPH) radical in rat brain homogenates (Yang et al., 2009). Oleracein E was the most potent compound in preventing the formation of

malondialdehyde (MDA) (Yang et al., 2009). Oleracone (figure 1 compounds 8) as novel alkaloid was first isolated from PA presented remarkably anti-inflammatory in model of lipopolysaccharide-stimulated macrophages (Meng et al., 2016).

4.3.Terpenoids

Portuloside A and B (figure 1 compounds 13, 14) and other monoterpene glycosides (figure 1 compounds 16, 17) (Sakai et al., 1996; Seo et al., 2003) and portulene which is a diterpene (figure 1 compounds 15) (Elkhayat et al., 2008) have been isolated from PA. In addition, PA contains triterpenes presented in figure 1 (compounds 18,19) (Xin et al., 2008).

4.4.Fatty acids

A plethora of investigations have suggested the beneficial effects of omega 3 fatty acids in atherosclerosis, coronary heart disease, and inflammatory disease (Connor, W. E. 2000*).* PA has been demonstrated to be one of the major plant sources of omega-3 fatty acids, particularly α-linolenic acid (up to 30%) and other essential fatty acids such as palmitoleic, palmitic, linoleic, oleic, stearic eicosapentaenoic and docosahexaenoic acids (Petropoulos et al., 2016, Zhou et al., 2015).

Other chemical constituents of PA are not unique to PA and have been found in many others plants. Purslane has been reported to be rich in vitamins like vitamin A, B-complex vitamins (riboflavin, niacin, and pyridoxine), ascorbic acid, and α-tocopherol. Minerals like potassium, magnesium, calcium, phosphorus, and iron and amino acids have also been isolated from this plant. Other compounds such as beta-carotene, portulacerebroside (figure 1, compound 20), catechol, bergapten glutathione, and melatonin have also been isolated from PA. Polysaccharides with potential therapeutic effects on diabetes were also found in PA (Petropoulos et al., 2016, Zhou et al., 2015).

Complete chemical constituents of PA are summarized in Table 2. The chemical structures of the main compounds are presented in figure 1.

5. Pharmacological Properties

PA is a well-known medicinal plant in traditional medicine systems with wide range of modern pharmacological activities. Antioxidant, hepatoprotective, analgesic, anti-inflammatory, wound healing, hypochloresterolemic and neuroactivity are among diverse pharmacological activities have been reported from PA. Summary of pharmacological activities of PA is presented in table 3. Detailed pharmacological activities are summarized below:

5.1. Renoprotective activity

There are several records on the traditional use of PA in kidney diseases and confirmed to be a renoprotective agent in recent studies. Gentamicin is an aminoglycoside with high toxicity in the kidney. Gentamicin may cause dangerous damages to renal brush border membrane (BBM), basolateral membrane (BLM) and lysosomes. It can also induce oxidative stress in renal tissues. Hence, the clinical use of this drug is limited due to adverse effects. In one research by Hozayen et al. (2011) 15 days oral administration (gastric intubation) of aqueous extract of PA (400 mg/kg, daily) and fish oil (5 mg/kg, daily) in two different groups of white male albino rats protected against gentamicin-induced (80 mg/kg, daily, toxic control group) nephrotoxicity. The gentamicin-increased plasma levels of urea, uric acid and creatinine were significantly decreased after administration of PA. Aqueous extract of PA is a rich source of antioxidant compounds. Hence, one proposal for renoprotective activity may be defensive activity against gentamicin-induced oxidative stress in renal tissues (Hozayen et al., 2011). In addition, dietary supplements which are enriched in ω-3 fatty acids, such as fish oil, can cause improvements in nutrition/energy metabolism; BBM integrity, antioxidant defenses and ^{32}Pi transport capacity and thus prevent gentamicin side effects. It is noteworthy that PA is

enriched in ω-3 and ω-6 fatty acids, which can result in higher protection against GM-induced nephrotoxicity than fish oil (Hozayen et al., 2011). However, the design of the study suffers from some critical issues. Ω-3 and ω-6 fatty acids are hydrophobic compounds and using the aqueous extract of PA in this study may affect total concentration of these compounds in the extract and reduce the activity. Moreover, the amount and composition of fatty acids were determined in petroleum ether extract, while the aqueous extract was used in animal study. They did not also specify the fatty acids content of the fish oil to make a better comparison between the extract and fish oil or conclude about the potency of the PA extract. The dose (400 mg/kg) has been used in this study is hardly in the range usually considered curative (Hozayen et al., 2011).

Cisplatin is another drug in market with nephrotoxic activity. Adjuvant therapy with an antioxidant has been suggested as a promising strategy to reduce chemical-induced adverse effects (Shirani et al., 2015). In a study by our group, the aqueous (0.2, 0.4 and 0.8 g/kg. intraperitoneal l[i.p.]) and ethanolic extracts (0.5, 1 and 2 g/kg, i.p.) of PA were administered 6-12 h prior to cisplatin (4 mg/kg, i.p.) injection to male Wistar rats (Karimi et al., 2010). Elevated blood urea nitrogen (BUN) and serum creatinine were used as biological markers of cisplatin-induced nephrotoxicity. Compared with control group (cisplatin alone), both extracts of PA significantly decreased BUN and creatinine levels. Histological examination also revealed the effectiveness of PA extracts. The proposed mechanism of action is almost similar to those discussed for gentamicin. However, activation of pro-inflammation factors is another mechanism of nephrotoxicity induced by cisplatin and anti-inflammatory effects of PA may be an additional protection mechanism (Karimi et al., 2010). Like previous study, the main problem in this study is the high dose has been used for protection. Another point is that, the toxicity of the extracts especially the high dose on kidney was not evaluated.

One of the most common microvascular complications of diabetes and the leading cause of end-stage renal disease is diabetic nephropathy. Administration of aqueous extract (300 mg/kg/day, p.o.) of PA for ten weeks to db/db mice decreased diabetic nephropathy by inhibition of renal fibrosis and inflammation (Lee et al., 2012). Moreover, it could significantly attenuate water intake, urine volume and plasma levels of glucose and creatinine compared to control group (Lee et al., 2012). More detailed mechanistic studies revealed that PA administration significantly ($p<0.01$) suppressed NF-κB p65 activation normally observed in db/db mice (Lee et al., 2012). The peroxisome proliferator-activated receptor-γ (PPAR- γ) agonist, rosiglitazone (10 mg/kg/day, p.o.) which is an antidiabetic agent for the treatment of type 2 diabetes, was chosen as a positive control. In this study like the previous one, phytochemical analysis of the extracts was not evaluated. Even though, this should be done to determine the active compound responsible for the observed mechanisms or to compare the potency with the positive control.

Evaluation of the antiurolithiatic activity of ethanolic extract of PA (100, 200 and 400 mg/kg/day for 15 days, orally) in rats, demonstrated that the extract could prevent ethylene glycol (0.75% v/v) and ammonium chloride (2% w/v) induced calcium oxalate uroliths formation by crystallization inhibition and diuretic activities (Kishore et al., 2013). PA could also restore elevated calcium, creatinine, urea and BUN plasma levels. The active treatment changed urinary back to normal (from 6 to 8) when compared to control group. Antispasmodic activity led to reduction of symptoms of renal stones (Kishore et al., 2013). The antiurolithiatic activity may be due to presence of potassium salts, flavonoids, phenolic compounds and saponins in aerial parts of the plant (Kishore et al., 2013). The effects of PA ethanolic extract at 400 mg/kg were comparable to Cystone (700 mg/kg) as a standard drug (Kishore et al., 2013).

In conclusion, the above-mentioned studies support renoprotective effects of PA in the traditional use. However, the doses are higher than normal ranges and hardly can be translated to human use.

5.2. Neuroactivity

Wang et al. (2007) studied the neuroprotective activities of PA extracts (0.25, 0.5 and 1 g/kg/day orally, 7 days) in hypoxia nerve tissues of male BALB/c mice (Wang et al., 2007). PA significantly increased the level of ATP, lactate dehydrogenase (LDH), phosphofructokinase (PFK) and pyruvate kinase (PK) of hypoxic brain cortices when compared with control group (received hypoxia without any treatment). All these effects lead to increment of available ATP for neurons. In addition, raise in erythropoietin mRNA expression was obviously higher in the group received PA as the active treatment (Wang et al., 2007). The authors suggested the increment might be the result of enhancement of the expression of hypoxia inducible factor-1 (HIF-1). The results of *in vitro* studies on PC-12 cells under hypoxic conditions with PA were in accordance with the *in vivo* study (Wang et al., 2007). In this study, hypoxic neuroprotective effects of PA extract were observed with high dose in both *in vivo* and *in vitro* studies. In addition, authors did not specify the kind of the extract they used in their investigation. Erythropoietin (EPO) decreases the risk of ischemic-hypoxic neurovascular damages and is also appreciated for its neuroprotective activity in brain. The ethanolic extract of PA (0.5, 1, or 2 mg/kg, orally, 7 days) at high doses stimulated the endogenous erythropoietin expression at both mRNA and protein levels by stabilizing HIFs**,** HIF-1α, in ICR mice brain (Wanyin et al., 2012). In addition, PA decreased the serum neuron specific enolase levels in hypoxic mice and the activity of caspase-3 in neurons, which reduced the pathological damages caused by the hypoxia condition. Also, PA could increase the neuron viability in hypoxia conditions (Wanyin et al., 2012).

In another study, Abdel Moneim (2013) evaluated neuroprotective activity of an aqueous juice of PA (1.5 mL/kg, 12 days) on brain damage caused by administration of rotenone in male Wister albino rats (Abdel Moneim, 2013). PA herbal aqueous juice could inhibit dopamine metabolism and apoptosis induction in the striatum of rats. The author suggested that PA may be a good candidate for future research treatment of Parkinson's disease or the other neurovascular brain damages. Rotenone is a potent inhibitor of mitochondrial complex I. Inhibition of this complex leads to production of O_2 free radicals that subsequently induces oxidative stress in neurons. Also in Parkinson's disease oxidative stress is the main cause of apoptosis induction in neurons (Abdel Moneim et al., 2013). Pre- post- and co-treatment of PA reduced nitrite/nitrate production, the expressions of inducible nitric oxide synthase (iNOS) and glutathione peroxidase, glutathione levels, LDH level and the numbers of NF-κB immunostaining neurons normally increased after rotenone administration (Abdel Moneim et al., 2013; Al-Quraishy et al., 2012). These findings show that the protective activity of PA is mainly due to its antioxidant activity. In this study, the authors did not specify the chemical constituents of the aqueous juice.

In another study, neuroprotective effects of PA aqueous extracts (2.5 to 10 mg/kg/day) were evaluated against D-galactose induced neurotoxicity in SD male mice (Hongxing et al., 2007). D-galactose-induced reductions in crossing, rearing/leaning and grooming activities were significantly reversed by administration of PA extract. PA significantly decreased the MDA level and increased superoxide dismutase (SOD) activity. In addition, the length of telomere was longer in PA treated group when compared with control group (D-galactose treated group). The proposed mechanism of action was a p21waf1-dependent and a p53-independent pathway (Hongxing et al., 2007). Betacyanins were identified as active ingredients responsible for neuroprotective activity (Wang and Yang, 2010).

Oral administration of the aqueous extract of PA leaves and stem (1.5 mL/kg) for 12 days to rats significantly decreased calcium concentration in brain cortex (Abdel Moneim et al., 2012). The extract increased dopamine level in cerebellum, cerebral cortex, thalamus and hypothalamus; norepinephrine and serotonin levels in cerebellum, pons, medulla oblongata, cerebral cortex, thalamus and hypothalamus (Abdel Moneim et al., 2012). However, administration of aqueous extract decreased dopamine, norepinephrine and serotonin levels in spinal cord. Acetyl cholinesterase was increased in all regions of brain except in the cerebellum. The authors linked these widespread effects of PA on neurotransmitters to high contents of ω-3 fatty acids and melatonin (Abdel Moneim et al., 2012). However, as it was mentioned earlier the solubility of ω-3 fatty acids in aqueous extracts is a subject of debate. The authors suggested the potential role of PA for regulation of neurotransmitters in many neurodegenerative disorders (Abdel Moneim et al., 2012).

A study by Xu and Shan (2014) demonstrated that polysaccharides (75, 150 and 300 mg/kg, respectively, 30 days) from PA dose dependently could increase the swimming time to fatigue of the male Kunming mice, as same as increasing the hepatic glycogen contents, while decreasing the blood lactic acid (BLA) and serum urea nitrogen (SUN) contents (Xu and Shan, 2014). This result indicated that polysaccharides from PA could decrease exhaustion induced by forced swimming, in mice (Xu and Shan, 2014).

On intraperitoneal administration, ethanolic extract of PA var. *sativa* (200 and 400 mg/kg), demonstrated a marked reduction in the locomotor activity in mice and an increase on the onset time of pentylenetetrazole-induced convulsions (Radhakrishnan et al., 2001).

In a randomized clinical trial in 60 chronic schizophrenic patients who received risperidone 6 mg/day and biperiden 4 mg/day, the effect of extract (1g, daily) of PA on psychological symptoms was studied (Parvin et al., 2013). At the end of the treatment (8 weeks), the mean score of positive and negative symptoms were significantly lower in treated group. The

authors concluded that PA can be an effective adjuvant therapy to respridone for improvement of psychological condition of chronic schizophrenia (Parvin et al., 2013).

5.3. Muscle relaxant effects

The skeletal muscle relaxation action of the aqueous extract of PA, when administered orally or intraperitoneally in rats, was evaluated by the prolongation of pull-up time (Parry et al., 1987). The i.p. route was more effective than the oral one. The extract (200-1000 mg/kg, i.p.) showed more effective skeletal muscle relaxant activity when compared with diazepam (40 mg/kg, i.p.), chlordiazepoxide (20 mg/kg, i.p.), and dantrolene sodium (30 mg/kg, oral). The effects of aqueous, methanol and dialysable extracts of PA leaves and stems were comparable with those of methoxyverapamil (D-600) and dantrolene sodium regarding inhibition of twitch tension on the phrenic nerve-hemidiaphragm of the rat and contracture induced by nicotinic agonists on rectus abdominis of the frog (Parry et al., 1993). The extracts of PA, D-600 and dantrolene inhibited twitch tension due to indirect electrical stimulation on hemidiaphragm muscle via the phrenic nerve. Moreover, dantrolene and the extracts of PA inhibited twitch amplitude caused by direct muscle stimulation. D-600 and the extracts were more effective in decreasing the action of nicotinic agonist (acetylcholine, nicotine and carbachol)-induced contractures on the rectus abdominis muscle than dantrolene. For this reason, it is believed that the effect of PA extracts is similar to the effect of D-600 and dantrolene on frog rectus abdominis muscles and the rat hemidiaphragm; therefore, the muscle relaxant action of the extracts may be due to inhibition of transmembrane Ca^{2+} influx, interference with the inhibition of the release of intracellular Ca^{2+} or interference with the Ca^{2+}-induced Ca^{2+} release process from stores in the sarcoplasmic reticulum (Parry et al., 1993).

In Habtemariam *et al*. (1993) study, it is shown that the high concentrations of potassium ions cause neuromuscular function of extracts of PA (Habtemariam et al., 1993). Solvent fractionation of the crude ethanolic extract on the chick biventer cervicis demonstrated that augmentation of muscle paralysis is depended on increasing in polarity: i.e. water fraction > butanol > ethyl acetate nearly equal to crude extracts. By turns, in weight of dried extract, these fractions contained 28%, 18%, 12.2% and 9%, of potassium. When the water fraction (the most active fraction) is desalted, it has no neuromuscular function even at 10 times higher concentration from initial concentration (Habtemariam et al., 1993).

5.4. Metabolic effect

For the first time, it has been shown by Al–Chalabi (2009) that a single intraperitoneal injection of two proteinous compounds (at a dose of 77.5 mg/kg) of the aqueous extract of PA to adult male mice, caused a significant decrease in serum glucose, cholesterol, triglycerides (TGs) and total lipids level as well as glycogen levels in liver. In another study, it has been suggested that the mixture of PA and pumpkin seeds has hypolipidemic, hypotriglyceridemic and hypocholesterolemic effects after 6 weeks in liver and plasma of adult male albino rats (Sprague-Dawley) with a reduction in plasma low density lipoprotein cholesterol (LDL-C) and an increase in high density lipoprotein cholesterol (HDL-C) levels. Furthermore, it had an antiatherogenic effect due to a significant reduction in LDL/HDL ratio. They discovered that these functions may have been mediated by unsaturated fatty acids such as alpha linolenic acid presented in seed mixture (Barakat and Mahmoud, 2011).

PA is one of the best edible foods for diabetic patients due to its anti-hyperglycemic and anti-hyperlipidemic effects. It has been reported that the aqueous extract of PA (300 mg/kg/day, p.o.) can ameliorate diabetic vascular complications in male C57BL/6J mice after 10 weeks treatment (Lee et al., 2012b). Over expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin, matrix

metalloproteinase-2 (MMP-2), and endothelin-1 (ET-1) were observed in aortic tissues of untreated mice, which were markedly suppressed by PA administration (Lee et al., 2012b). The insulin immunoreactivity of the pancreatic islets has also been increased in PA treated mice compared with untreated mice (Lee et al., 2012b). This study demonstrated that diabetic mice treated with PA (300 mg/kg/day, p.o.), exhibited a reduction in plasma triglyceride levels, systolic blood pressure, blood glucose and level of LDL-C in plasma. Moreover, PA could increase plasma levels of HDL-C and insulin. Therefore, PA prevents the dysfunction and inflammation in diabetic vascular diseases (Lee et al., 2012b). In another study, an aqueous extract of PA (100 and 200 mg/kg) prevented from oxidative damage induced by high-fat-diet in male kunming mice (Chen et al., 2012). The administration of PA declined levels of blood and liver lipid peroxidation while increased the activities of antioxidant enzymes in blood and liver. Further investigations showed an increment in liver Leptin/β-actin and PPARα/β-actin (Chen et al., 2012).

In a triple-blinded, randomized, controlled trial, the effect of PA seeds (500 mg, twice a day) on dyslipidemia in 37 obese adolescents was studied (Sabzghabaee et al., 2014). PA treatment for 4 weeks significantly reduced LDL-C and TG levels compared to the control group. The herbal treatment well-tolerated in all patients and can have positive effects on serum lipids profile (Sabzghabaee et al., 2014).

Treatment with 400 mg/kg polysaccharides from PA (CPP) for 28 days similar to glibenclamide (4 mg/kg) resulted in a significant decrease in the concentration of fasting blood glucose (FBG), TG and total cholesterol in diabetic male Kunming mice induced by alloxan. CPP can modulate the metabolism of blood lipid profile and glucose in diabetes mellitus without any physical or behavioral signs of toxicity (Gong et al., 2009).

Another study has shown, although streptozotocin (STZ) can induce hyperglycemia, after 3 weeks of orally using polysaccharide fraction of PA (25 and 50 mg/kg), reduction in

thiobarbituric acid reactive substances and blood glucose of diabetic Sprague–Dawley rats were observed, as well as an increase in total reduced glutathione levels. This study showed that treatment with CPP ameliorates the STZ-induced diabetic complications in rats, which was comparable to standard tolbutamide (10 mg/kg, p.o.) (Sharma et al., 2012).

El-Sayed (2011) reported that oral administration of 5 g of PA seeds twice daily could reduce the liver enzymes and blood glucose in diabetic patient with similar effects to metformin (El-Sayed, 2011). However, 1,500 mg of metformin/day did not have a significant effect on HDL-C, LDL-C, and alkaline phosphatase (ALP) levels. Therefore, PA seeds can be used as an effective and safe adjuvant therapy for Type-2 diabetic subjects. This study also showed that PA could reduce the insulin resistance because of its flavonoid, polyunsaturated fatty acid and polysaccharide contents (El-Sayed, 2011). In addition, PA has α-amylase (Odhav et al., 2013) and α-glucosidase (Salehi et al., 2013) inhibitory effect and therefore is able to reduce blood glucose.

One of the main complications of diabetes is vascular inflammation which is playing a key role in the pathogenesis and progression of atherosclerosis. Furthermore, recent investigations have evidenced that inflammatory events contribute to each stage of the development of clinically significant atherosclerosis. New researches show the effect of aqueous extract of PA (10–100 μg/mL) as a preventer for tumor necrosis factor (TNF)-α-induced vascular inflammatory process in the human umbilical vein endothelial cell (HUVEC) and it has TNF-α and IL-6 inhibitory activity (Lee et al., 2012a; Xiao et al., 2005). In a dose-dependent manner, PA significantly suppressed TNF-α-induced over-expression of adhesion molecules and reactive oxygen species (ROS) production. Furthermore, it reduced the increased adhesion of HL-60 cells to TNF-α-induced HUVEC. Taken together, PA inhibited intracellular ROS production and NF-κB activation as well as the reduction of adhesion

molecule expression in TNF-α-induced HUVEC. As a result, it is understood that it can prevent the vascular inflammatory process (Lee et al., 2012a).

In a randomized, double-blind, placebo-controlled clinical trial, effect of PA extract (180 mg/day Portusana^{TM}) on glucose control, blood pressure, and lipid profile in 63 adults with type 2 diabetes mellitus was studied (Wainstein et al., 2016). After 12 weeks of treatment, systolic blood pressure and HbA1c were significantly declined compared to control group (Wainstein et al., 2016). These findings show that PA can be a good adjuvant therapy in patients with type 2 diabetes mellitus.

In a randomized controlled cross‐over clinical trial by Zakizadeh *et al*., (2015), the effect of 10 g/day of PA seeds (5 weeks) on total antioxidant capacity, MDA and oxidized‐low density lipoprotein was evaluated in patients with type 2 diabetes. After 5 weeks, no significant effect was observed and the authors stated that PA treatment couldn't result in improved oxidative stress (Zakizadeh et al., 2015).

PA can be a valuable adjuvant therapy in patients with deleterious complications of metabolic syndrome including diabetes and cardiovascular disease. More clinical trials in the future are needed to unravel more aspects of the effect.

5.5. Hepatoprotective effects

PA has been long used as a medication against liver injury. In a study by Abd El-Azime *et al*. (2014), it has been shown that a single dose of 6 Gy gamma rays can increase LDL-C, total cholesterol, TG, aspartate and alanine transaminase (AST, ALT), ALP, creatinine, bilirubin, urea and uric acid (Abd El-Azime et al., 2014). Moreover, liver, kidney and heart MDA were significantly elevated but nitric oxide, catalase, SOD, and HDL-C were reduced in irradiated rat. Co-administration of aqueous extract of PA (400 mg/kg) and fish oil (60 mg/kg body weight) via gastric intubation for 15 days significantly reduced lipids alteration, liver and

kidney functions as well as oxidative stress in irradiated male albino rats (Abd El-Azime et al., 2014).

Intraperitoneal injection of carbon tetrachloride (CCl_4) can induce hepatotoxicity in male Wistar rats. However, PA ethanolic extract (0.005, 0.01, 0.05, 0.1, and 0.15 g/kg, intragastrically) at different doses restored the levels of hepatic marker enzymes and SOD to normal after 30 days treatment (Eidi et al., 2015). Hepatic fibrosis is one of the most common reasons for bile duct ligation and it also causes cholestasis-induced liver fibrosis. PA (400 mg /kg, orally, 4 weeks) due to its antioxidative action and decreasing the collagenolytic activity, expression of profibrogenic cytokines, and activation of hepatic stellate cells could prevent or cure cholestasis-induced liver fibrosis in adult female albino rats. In this study, PA showed the same effects as silymarin in restoring the liver function to normal (Ali et al., 2011). For these reasons, PA can be used to treat this disease as same as alpha tocopherol. However, according to this study, it is suggested that PA prophylactic properties are better than its therapeutic ones (Ali et al., 2011). Moreover, disarrangement of normal hepatic cells with intense vacuolization of cytoplasm, centrilobular necrosis and fatty degeneration in rats were treated with ethanolic extract of PA after intoxication by CCl_4 (Ahmad et al., 2013). Clerodene diterpene portulene, which is a newly found compound from PA may have hepatoprotective effects (Elkhayat et al., 2008).

5.6.Reducing abnormal uterine bleeding (AUB)

In a study by Shobeiri *et al*., PA was used for the treatment of abnormal uterine bleeding (AUB) (Shobeiri et al., 2009). In this study, ten premenopausal women with AUB including metrorrhagia, menorrhagia, polymenorrhea and intermenstrual bleeding who had not responded to standard drugs were given 5 g of PA seeds powder in a glass of water orally. Eight (80%) patients reported that the volume and duration of bleeding had reduced and their patterns of periods had normalized. However, it had been ineffective in two (20%) patients. It

did not have adverse effects and AUB did not recur in the patients who responded to treatment (Shobeiri et al., 2009).

5.7. Antimicrobial effects

Antimicrobial effect of flavonoids of PA on the food-borne and spoilage pathogens was tested. The results indicated that it could inhibit the growth of molds such as *Penicillium* sp., *Rhizopus* sp., *Mucor racemosus* and *Aspergillus niger*. However, it could not inhibit the growth of *Candida tropicalis* and *Saccharomyces cerevisiae* (Dan, 2006). Another study reported the antifungal activity of PA extracts against hyphal growth of *Aspergillus* and *Trichophyton* and the yeast *Candida* (Oh et al., 2000). Also, the antifungal activity of PA extracts against hyphal growth of varied fungi was examined. The antifungal activity of each fraction of PA was evaluated based on the dynamic hyphal growth response curves of test fungi *Trichophyton* and *Aspergillus* and the yeast *Candida*. A crude sample obtained by ethyl acetate extract showed a significant effect against dermatophytes of the genera *Trichophyton* (Oh et al., 2000). This plant could effectively inhibit the growth of bacteria such as *Neisseria gonorrhea, Staphylococcus aureus, Escherichia coli* and *Bacillus subtilis* (Elkhayat et al., 2008). Water and 80% ethanolic extracts of PA showed high antimicrobial effects against *Helicobacter pylori, Staphylococcus epidermidis* and *Streptococcus mutans* (Cho et al., 2008). Linoleic and oleic acids from PA showed synergistic antibacterial activity when combined with erythromycin against methicillin-resistant *Staphylococcus aureus* (MRSA). The possible mechanism of action for these two compounds was inhibition of efflux pumps (Chan et al., 2015).

5.8. Anti-fertility effect

The administration of flavonoid extract of air-dried aerial part of PA has shown encouraging abortifacient activities and anti-implantation at high doses (500 mg/kg) on female albino rats

(Hanumantappa et al., 2014). They also assessed flavonoid effects on ovary and uterus (genital organs). The flavonoid content could change estrous cycle with a prolonged diestrus. It could increase the ovary weight and uterine muscle weight. These hormonal changes in body, lead to its anti-fertility effect. So, total flavonoids of this plant have potential anti-fertility effect (Hanumantappa et al., 2014).

In Nayaka and Londonkar (2014) study, dried chloroform extract of PA (250 and 500 mg/kg) was administered orally to female albino rats. The anti-estrogenic activity, anti-ovulatory activity and effect on uterine muscle weight were evaluated. They demonstrated that this extract affects ovulation by reducing number of ova in ovary and can cause significant increase in uterus and ovary weight and thus can cause anti-fertility effect (Nayaka and Londonkar, 2014).

5.9. Gastric antiulcerogenic Activity

Gastroprotective activity of 50% ethanolic extract of PA (50-150 mg/kg, orally) has been investigated in acute gastric ulcer induced by ethanol, aspirin, cold restraint stress, pyloric ligation and chronic ulcers induced by acetic acid models in rats (Kumar et al., 2010). PA showed significant protective and healing effects against gastric ulcer. This study suggested that the mechanism of PA effect is due to preventing the oxidative damage of gastric mucosa through significant decrease in superoxide dismutase and by blocking lipid peroxidation as well as an increase in catalase activity (Kumar et al., 2010). Also, PA significantly decreased the acid and pepsin secretion and increased the synthesis of mucus. These effects lead to prevention of physical damage and back diffusion of hydrogen ions (Kumar et al., 2010).

5.10. Anti-inflammatory and analgesic effects

The administration of 10% ethanolic extract (200 and 400 mg/kg i.p.) of PA to Wistar rats reduced the hind paw inflammation induced by carrageenan (Chan et al., 2000). In addition,

the anti-inflammatory potential of PA was assessed using the cotton pellet method within 6 days of subacute treatment. The results were comparable to diclofenac as a well-known anti-inflammatory drug (Chan et al., 2000). However, the underlying mechanism was not studied. A research on compounds isolated from PA showed that trans-docosanoyl ferulate (a phenyl propanoid ester) can inhibit cyclooxygenase 1 and 2 with IC_{50} values of 40.2 µM and 1.6 mM, respectively (Kim et al., 2012).

Kim, et al. (2012) found a TNF-α dependent mechanism for anti-inflammatory effects of PA (Kim, et al., 2012). In the human umbilical vein endothelial cell (HUVEC), an aqueous extract of PA could significantly inhibit TNF-α-induced vascular inflammatory process. PA inhibited TNF-α-induced ROS production and translocation of p65 NF-κB to the nucleus. In addition, mRNA expressions of monocyte chemoattractant protein-1 and interleukin-8 were significantly reduced with PA treatment (Kim, et al., 2012).

Pain caused by tissue damages or infections is a common feature of the inflammatory process which stimulates changes in local blood flow, peripheral nerve fibers, and vascular permeability (Vahdati Hassani et al., 2015). Ethanolic extract of the dried leaves and stem (aerial parts) of PA ssp. *sativa* (200 and 400 mg/kg) showed significant analgesic and anti-inflammatory activities after topical and intraperitoneal administration when compared with the diclofenac sodium as the positive control (Chan et al., 2000). However, these effects were not shown after oral administration of PA (Chan et al., 2000). It also has the antinociceptive activity in rats using tail flick method. PA var. *sativa* can have various effects on both the peripheral and central nervous system. The anti-nociceptive activity of the extract was attenuated by naloxone pre-treatment, indicating the involvement of opioid receptors in its antinociceptive effects (Miladi et al., 2005).

5.11. Cytotoxic activity

Generally, studies showed that PA is not a remarkable cytotoxic plant. Four studies showed no or weak cytotoxic activities for methanol extract of PA (Antoun et al., 1999; Payudara et al., 2013; Shabsoug et al., 2008; Yen et al., 2001). Two novel triterpenoids isolated from PA showed weak cytotoxicity in MTT assay (Salehi et al., 2013). Sulfated derivatives of for polysaccharides isolated from water soluble extract of PA showed weak cytotoxic activities in a human liver cancer cell line (HepG2) with IC_{50} values ranging from 100 to 2000 µg/mL (Chen et al., 2010). Four alkaloids (**6**, **7**) from PA were slightly cytotoxic against a human long cancer cell line (A549) (Tian et al., 2014).

6. Pharmacokinetic studies

In a study by Cheng *et al*. pharmacokinetic profiles of hesperidin, caffeic acid, ferulic acid and *p*-coumaric acid were evaluated after intravenous administration of PA extract to rats (Cheng et al., 2012). Volumes of distribution for these compounds were 0.044, 0.041, 0.077 and 0.044 L/kg, while the terminal half-lives were 99.6, 40.7, 65.5 and 39.9 min, respectively (Cheng et al., 2012). 2.0, 0.33 and 0.25 h after oral administration, hesperidin, ferulic acid and *p*-coumaric reached their maximum plasma concentration. The C_{max} were 0.196, 0.988 and 1.24 µg/mL, respectively (Cheng et al., 2012). The pharmacokinetic profile of the anti-inflammatory alkaloid, oleracone was also studied (Meng et al., 2016). The results showed the following profile for this compound: distribution half-life, IV 0.22 min and oral 5.23 min; elimination half-life, IV 15.28 min and oral 61.34 min; clearance, IV 0.042 L/min/kg and oral 0.056 L/min/kg (Meng et al., 2016).

In a more recent study pharmacokinetics and biodistribution of aurantiamide and aurantiamide acetate, two alkaloids from PA were studied after oral administration to rat (Chen et al., 2016). The results of pharmacokinetic studies for are given as follows: the first peak time, 0.18 and 21h; the second peak time, 2.67 and 0.75h; half-life, 25.34 and 36.49 h; C_{max} 3.50 and 1.61 µg/L, respectively (Chen et al., 2016).

7. Safety

As it was mentioned elsewhere, PA did not show cytotoxic effects in *in vitro* studies and the IC_{50} values where more than 100 µg/mL which are pharmacologically considered inactive (Antoun et al., 1999; Payudara et al., 2013; Shabsoug et al., 2008; Yen et al., 2001).

Acute toxicity studies of the methanolic extract of PA on mice revealed that PA is moderately toxic with LD_{50} value of 1853 mg/kg. In histopathological studies, the methanolic extract showed hepatic and renal toxicities (Musa et al., 2007). Based on these data, PA has a high therapeutic index. However, more studies especially on chronic toxicity of PA are needed.

Most of clinical trials have not reported any adverse effects. Generally, PA is well tolerated in the most of patients. However, skin rash, thyroiditis and facial nerve palsy reported in three patients, respectively (Leung et al., 2006). In another clinical trial constipation was reported as the only side effect related to PA consumption (Wainstein et al., 2016).

8. Conclusion

PA has a long history of use in traditional medicine systems for many ailments (Osbaldeston, 2000). The present article presents an overview of the botany, traditional uses, phytochemistry, pharmacology and toxicity of PA. *In vitro* studies and *in vivo* experiments on PA have revealed many biological activities such as renoprotective, neuroprotectiv, muscle relaxant, anti-inflammatory and analgesic, cytotoxic, anti-ulcerogenic, anti-fertility, antimicrobial, hepatoprotective, anti-AUB, hypolipidemic, hypotriglyceridemic and hypocholesterolemic activities. These observations can help to produce hypothesis for potential therapeutic effects of PA which have to be proved through ongoing clinical trials. However, a number of clinical trials revealed the promising effects of PA in the treatment of chronic schizophrenia, hypertension, hyperglycemia and dyslipidemia. The current clinical evidence suggests that oral dose of 180 mg/day of PA extract is possibly safe and effective in the treatment of hypertension and hyperglycemia. Moreover, administration of a daily oral

dose of 1g may safely improve psychological condition in chronic schizophrenic patients as well as dyslipidemia. Some pharmacological activities of PA including anti-inflammatory, anti-fatigue activity, hepatic glycogen and glutathione levels enhancing and blood glucose, BLA and SUN reducing properties have been reported to be attributed to PA polysaccharides content. Unsaturated fatty acids such as alpha linolenic acid are also responsible for some of PA activities including hypolipidemic, hypotriglyceridemic and hypocholesterolemic activities.

However, many pharmacological aspects of PA and its major constituents are yet to be elucidated. Therefore, mechanisms of actions, clinical effectiveness, pharmacokinetic properties and proper dosages would need to be further investigated. Furthermore, despite the presence of a large body of scientific evidence regarding the biological and medicinal properties of PA, several gaps in our understanding of the applications of this plant still exist. Firstly, most frequent traditional uses of PA seems to be the treatment of headache, inflammations, teeth problems, stomach illnesses, respiratory diseases, worms, fever, scurvy and epistaxis, wounds and ulcers. However, many of the mentioned uses have been overlooked by recent studies. For instance, despite a majority of traditional sources have emphasized on beneficial effects of PA on respiratory diseases, teeth problems and gastrointestinal problems, rare studies have focused on these activities and the mechanisms of actions underlying them. Therefore, it seems that these uses should be considered in future studies.

Secondly, some of the pharmacological activities of PA reported by *in vitro* and animal studies have been observed in doses that can hardly be translated to clinical practice. For instance, nephroprotective and antiurolithiatic properties of PA has been observed in high doses of 0.4 to 2 g/kg which are too high for replication in human studies. Therefore,

although PA has been considered a very safe medicinal plant, high doses of PA extracts must be carefully administered in human studies.

Thirdly, a number of studies addressed Pharmacokinetic aspects of a few active ingredients present in PA. However, data on the pharmacokinetic aspects of the whole extracts of the plant are scarce and additional studies should be conducted to evaluate the absorption, distribution and metabolism of PA extracts in human body.

Finally, many pharmacological activities of PA have been observed through *in vitro* and animal studies. However, despite the promising results have been obtained from these studies, supporting clinical trials and human observations are scarce. Therefore, conducting additional clinical studies to support the biological activities of PA seems to be necessary.

In conclusion, future studies must investigate pharmacological activities related to the overlooked traditional uses of PA especially on headache, respiratory and gastrointestinal diseases. Future studies also should elucidate the exact mechanisms of actions of PA and its major bioactive phytochemicals. Clinical trials have to be conducted to evaluate efficacy, safety, proper dosage and pharmacokinetic aspects of PA in order to develop safe and effective dosage forms from this plant.

9. Conflict of interest

The authors declared no conflict of interest.

References:

Abbasi A.M., Shah M.H., Khan M.A., 2015. Wild edible vegetables of lesser himalayas. Springer:125.

Abd El-Azime, A.S., Hussein, E.M., Ashry, O.M., 2014. Synergestic effect of aqueous purslane (Portulaca oleracea L.) extract and fish oil on radiation-induced damage in rats. Int. J. Radiat. Biol. 90, 1184-1190.

Abdel Moneim, A.E., Al Nasr, I., Dkhil, M.A., Al-Quraishy, S., 2012. Neuronal activities of *Portulaca oleracea* in adult rats. J. Med. Plant Res. 6, 3162-3168.

Abdel Moneim, A.E., 2013. The neuroprotective effects of purslane (*Portulaca oleracea*) on rotenone-induced biochemical changes and apoptosis in brain of rat. CNS Neurol. Disord. Drug Targets 12, 830-841.

Abdel Moneim, A.E., Dkhil, M.A., Al-Quraishy, S., 2013. The potential role of Portulaca oleracea as a neuroprotective agent in rotenone-induced neurotoxicity and apoptosis in the brain of rats. Pestic. Biochem. Physiol. 105, 203-212.

Ahmad, M., Itoo, A., Baba, I., Jain, S., Saxena, R., 2013. Hepatoprotective activity of *Portulaca oleracea* Linn. on experimental animal model. Int. J. Pharm. Pharm. Sci. 5, 267-269.

Al-Asmari AK, Al-Elaiwi AM, Athar MT, Tariq M, Al Eid A, Al-Asmary SM., 2014. A review of hepatoprotective plants used in saudi traditional medicine. Evid. Based Complement. Alternat. Med. 2014:890842.

al-Nafis, I., 1999. Al-Shamel fi al-Sinaat al -Tibbiah (Comprehensive Book on the Art of Medicine). al-Majma' al-Thaqafi (Publications of the Cultural Centre), Abu Dhabi.

Al-Quraishy, S., Dkhil, M.A., Abdel Moneim, A.E., 2012. Protective effects of *Portulaca oleracea* against rotenone mediated depletion of glutathione in the striatum of rats as an animal model of Parkinson's disease. Pestic. Biochem. Physiol. 103, 108-114.

Al-Zahrawi, A., 2004. Al-Tasrif. Kuwait foundation for the advancement of sciences, Kuwait.

Al–Chalabi, N.S., 2009. Effect of proteinous compounds from *Portulaca oleracea* L. plant on some biochemical parameters in mice. Med. J.of Babylon 3, 506-510.

Albala, K., 2011. Food cultures of the world encyclopedia. ABC-CLIO.

Ali, S.I., Said, M.M., Hassan, E.K., 2011. Prophylactic and curative effects of purslane on bile duct ligation-induced hepatic fibrosis in albino rats. Ann. Hepatol. 10, 340-346.

Amiri MS, Joharchi MR., 2013. Ethnobotanical investigation of traditional medicinal plants commercialized in the markets of mashhad, iran. Avicenna J. Phytomed. 3, 254-271.

Anonymous, 1989. The Ayurvedic Pharmacopoeia of India, Part-I, vol.-2, first English ed., Government of India, Ministry of Health and Family Welfare, Department of Health, New Delhi.

Antoun, M., Martinez, E., Caballero, R., Oquendo, I., Proctor, G., Weislow, O., McCloud, T., Kiser, R., Staley, P., Clanton, D., 1999. Evaluation of the flora of Puerto Rico for in vitro cytotoxic and anti-HIV activities. Pharm. Biol. 37, 277-280.

Anusha, M., Venkateswarlu, M., Prabhakaran, V., Taj, S.S., Kumari, B.P., Ranganayakulu, D., 2011. Hepatoprotective activity of aqueous extract of *Portulaca oleracea* in combination with lycopene in rats. Indian J. Pharmacol. 43, 563-567.

Aqili Khorasani, MH., 1992. Makhzan al-Adwiah (Drug Treasure). Reprinted from a copy which was printed in Calcutta dated in 1844. Enqelab-e Eslami Publishing and Educational Organization, Tehran.

Aqili Khorasani, M.H., 2007. Qarâbâdin Kabir (The Grand Pharmacopeia) Research Institute for Islamic and Complementary Medicine (RICM), Tehran.

Banerjee, G., Mukherjee, A., 2003. Antibacterial activity of a common weed, *Portulaca oleracea* L. Geobios 30, 143-144.

Barakat, L.A., Mahmoud, R.H., 2011. The antiatherogenic, renal protective and immunomodulatory effects of purslane, pumpkin and flax seeds on hypercholesterolemic rats. N. Am. J. Med. Sci. 3, 411-417.

Bachar M, Zidane L, Rochdi A. Ethno-medicinal and traditional phytotherapy of plants used in bouhachem natural regional park "rif of morocco"-case of tazroute district-plantes médicinales et phytothérapie traditionnelle utilisées au niveau du parc naturel régional de bouhachem «rif du maroc»-cas de la commune rurale de tazroute.

Belcheff, E., 2012. A Medical Intuitive Reveals the Wonders of Purslane. Polished Publishing Group.

Bello, S., Ahanchédé, A., Gbèhounou, G., Amadji, G., Aho, N., 2013. Diversité floristique, ethnobotanique et taxonomie locale des mauvaises herbes de l'oignon au nord-est du bénin. Tropicultura 31:143-152.

Béné, K., Camara, D., Fofie, N. GBY, Kanga, Y., Yapi, A.B., Yapo, Y.C., Ambe, S.A., Zirihi, G.N., 2016. Étude ethnobotanique des plantes médicinales utilisées dans le département de transua, district du zanzan (côte d'ivoire). J. Anim. Plant. Sci. 27,4230-4250.

Benkhnigue, O., Zidane, L., Fadli, M., Elyacoubi, H., Rochdi, A, Douira, A., 2010. Etude ethnobotanique des plantes médicinales dans la région de mechraâ bel ksiri (région du gharb du maroc). Acta Bot.Barcinonensia 53,191-216.

Bosi, G., Guarrera, P.M., Rinaldi, R., Bandini Mazzanti, M., 2009. Ethnobotany of purslane (*Portulaca oleracea* L.) in Italy and morfo-biometric analyses of seeds from archaeological sites of Emilia Romagna (Northern Italy). Plants and Culture: seeds of the cultural heritage of Europe. EdiPuglia, Bari, 129-139.

Boulos, L., Hadidi, M.N., Gohary, M., 1984. weed flora of Egypt. American University in Cairo Press.

Brussell, E.D., 2004. Medicinal plants of mt. Pelion, greece. Econ. Bot. 58,S174-S202.

Byrne, R., Mcandrews, J., 1975. Pre-columbian purslane (*portulaca oleracea* L) in the new world. Nature 253, 726 - 727

Carrio E, Valles J. 2012. Ethnobotany of medicinal plants used in eastern mallorca (balearic islands, mediterranean sea). J. Ethnopharmacol. 141,1021-40.

Cakilcioglu, U., Turkoglu, I., 2010. An ethnobotanical survey of medicinal plants in sivrice (elazig-turkey). J. Ethnopharmacol. 132,165-75.

Chan, B.C., Han, X., Lui, S.L., Wong, C., Wang, T.B., Cheung, D.W., Cheng, S.W., Ip, M., Han, S.Q., Yang, X.S., 2015. Combating against methicillin-resistant Staphylococcus aureus–two fatty acids from Purslane (*Portulaca oleracea* L.) exhibit synergistic effects with erythromycin. J. Pharm. Pharmacol. 67, 107-116.

Chan, K., Islam, M.W., Kamil, M., Radhakrishnan, R., Zakaria, M.N.M., Habibullah, M., Attas, A., 2000. The analgesic and anti-inflammatory effects of *Portulaca oleracea* L. subsp. sativa (Haw.) Celak. J Ethnopharmacol. 73, 445-451.

Chapman, J., Stewart, R.B., Yarnell, R.A., 1973. Archaeological evidence for precolumbian introduction of *Portulaca oleracea* and *Mollugo verticillata* into Eastern North America. Econ. Bot. 28, 411-412.

Chashti, M.A.K., 1884. Exir-e-Azam, 2 ed. Nami Monshi Nolkshur, Delhi

Chen, B., Zhou, H., Zhao, W., Zhou, W., Yuan, Q., Yang, G., 2012. Effects of aqueous extract of *Portulaca oleracea* L. on oxidative stress and liver, spleen leptin, PARα and FAS mRNA expression in high-fat diet induced mice. Mol. Biol. Rep. 39, 7981-7988.

Chen, C.J., Wang, W.Y., Wang, X.L., Dong, L.W., Yue, Y.T., Xin, H.L., Ling, C.Q., Li, M., 2009. Anti-hypoxic activity of the ethanol extract from *Portulaca oleracea* in mice. J. Ethnopharmacol.124, 246-250.

Chen, J., Shi, Y.-P., Liu, J.-Y., 2003. Determination of noradrenaline and dopamine in Chinese herbal extracts from *Portulaca oleracea* L. by high-performance liquid chromatography. Mol. Biol. Rep. A 1003, 127-132.

Chen, J., Shi, Y.P., Liu, J.Y., 2003. Determination of noradrenaline and dopamine in Chinese herbal extracts from *Portulaca oleracea* L. by high-performance liquid chromatography. J. Chromatogr. A 1003, 127-132.

Chen, L., Liu, Y., Jia, D., Yang, J., Zhao, J., Chen, C., Liu, H., Liang, X., 2016. Pharmacokinetics and biodistribution of aurantiamide and aurantiamide acetate in rats after oral administration of *Portulaca oleracea* L. extracts. J. Agric. Food Chem. 64, 3445-3455.

Chen, T., Wang, J., Li, Y., Shen, J., Zhao, T., Zhang, H., 2010. Sulfated modification and cytotoxicity of *Portulaca oleracea* L. polysaccharides. Glycoconj J. 27, 635-642.

Cheng, Z., Wang, D., Zhang, W., Du, Y., Wang, Y., Zhai, Y., Ying, X., Kang, T., 2012. LC determination and pharmacokinetic study of the main phenolic components of *Portulaca oleracea* L. extract in rat plasma after oral administration. Nat. Prod. Res. 26, 2247-2250.

Cheng, Z., Xie, M., Zhang, W., Cheng, L., Du, Y., Wang, Y., Ying, X., Kang, T., 2012. HPLC method for the simultaneous determination of four compounds in rat plasma after intravenous administration of *Portulaca oleracea* L. extract. Brazilian Journal of Pharmaceutical Sciences 48, 163-170.

Chinese Pharmacopoeia Commission, 2010. The Pharmacopoeia of the People's Republic of China (2010 English Edition), 1, China Medical Science Press, Beijing, China.

Cho, Y.J., Ju, I.S., Kwon, O.J., Chun, S.S., An, B.J., Kim, J.H., 2008. Biological and antimicrobial activity of *Portulaca oleracea*. J. Korean. Soc. Appl. Biol. Chem. 51, 49-54.

Connor, W. E. 2000. Importance of n− 3 fatty acids in health and disease. Am. J. Clin. Nutr. 71, 171S-175S.

Dan, Z., 2006. Study on Antimicrobial Effect of Flavonoids from *Portulace oleracea* L. J. Anhui Agri. Sci. 34, 7.

De Feo V., Aquino R., Menghini A., Ramundo E., Senatore F., 1992. Traditional phytotherapy in the peninsula sorrentina, campania, southern italy. J. Ethnopharmacol. 36,113-125.

Della A, Paraskeva-Hadjichambi D, Hadjichambis A. 2006. An ethnobotanical survey of wild edible plants of paphos and larnaca countryside of cyprus. J. Ethnobiol. Ethnomed. 2,34.

Dweck, A.C., 2001. Purslane (*Portulaca oleracea*)-the global panacea. Pers. Care Mag. 2(4), 7-15.

Eidi, A., Mortazavi, P., Moghadam, J.Z., Mardani, P.M., 2015. Hepatoprotective effects of *Portulaca oleracea* extract against CCl4-induced damage in rats. Pharm. Biol. 53, 1042-1051.

El-Ghonemy, A., 1993. Encyclopedia of Medicinal Plants of the United Arab Emirates. University of United Arab Emirates Press, UAE, 568.

El-Sayed, M.I., 2011. Effects of *Portulaca oleracea* L. seeds in treatment of type-2 diabetes mellitus patients as adjunctive and alternative therapy. J. Ethnopharmacol. 137, 643-651.

Elkhayat, E.S., Ibrahim, S.R., Aziz, M.A., 2008. Portulene, a new diterpene from *Portulaca oleracea* L. Journal of Asian Nat. Prod. Res. 10, 1039-1043.

Evelyn, J., 1699. Acetaria: A Discourse of Sallets Gale

Ghasemi Pirbalouti, A., Momeni, M., Bahmani, M., 2013. Ethnobotanical study of medicinal plants used by kurd tribe in dehloran and abdanan districts, ilam province, iran. Afr. J. Tradit. Complement. Altern. Med. 10,368-85

Gong, F., Li, F., Zhang, L., Li, J., Zhang, Z., Wang, G., 2009. Hypoglycemic effects of crude polysaccharide from purslane. Int. J. Mol. Sci. 10, 880-888.

Gonzalez-Tejero, M.R., Casares-Porcel, M., Sanchez-Rojas, C.P., Ramiro-Gutierrez, J.M., Molero-Mesa, J, Pieroni, A., Giusti, ME, Censorii, E., De Pasquale, C., Della, A., Paraskeva-Hadijchambi, D., Hadjichambis, A., Houmani, Z., El-Demerdash, M., El-Zayat, M., Hmamouchi, M., Eljohrig, S., 2008. Medicinal plants in the mediterranean area: Synthesis of the results of the project rubia. J. Ethnopharmacol. 116,341-57.

Guarrera, P.M., 2003. Food medicine and minor nourishment in the folk traditions of central italy (marche, abruzzo and latium). Fitoterapia 74,515-44.

Guarrera PM, Savo V., 2013. Perceived health properties of wild and cultivated food plants in local and popular traditions of italy: A review. J. Ethnopharmacol. 146,659-80.

Habtemariam, S., Harvey, A.L., Waterman, P.G., 1993. The muscle relaxant properties of *Portulaca oleracea* are associated with high concentrations of potassium ions. J. Ethnopharmacol. 40, 195-200.

Hanumantappa, B.N., Ramesh, L., Umesh, M., 2014. Evaluation of Potential Antifertility activity of Total Flavonoids, Isolated from *Portulaca oleracea* L on female albino rats. Int. J. PharmTech. Res. 6, 783-793,

Hongxing, Z., Nancai, Y., Guofu, H., Jianbo, S., Yanxia, W., Hanju, H., Qian, L., Wei, M., Yandong, Y., Hao, H., 2007. Neuroprotective effects of purslane herb aquenous extracts against D-galactose induced neurotoxicity. Chem. Biol. Interact. 170, 145-152.

Hozayen, W., Bastawy, M., Elshafeey, H., 2011. Effects of aqueous purslane (*Portulaca oleracea*) extract and fish oil on gentamicin nephrotoxicity in Albino rats. Nature Sci. 9, 47-62.

Ibn Sina, H, 1987. A. Al-Qanun fi'l-Tibb (Canon of Medicine). I.H.M.M.R. Printing Press, New Delhi.

Iserin, P., Masson, M., Restellini, J., 2001. Larousse encyclopédie des plantes médicinales: identification, préparations, soins. Larousse, Paris, 254.

Jorjani, SE., J., 1976 Zakhireh Kharazmshahi (Treasure of Kharazmshahi)Saeedi Sirjani A.A., editor. The lranian Culture Foundation.vol3. 462, Photo print of the manuscript dated 1206 A.D Tehran.

Joshi, A.R., Joshi, K., 2000. Indigenous knowledge and uses of medicinal plants by local communities of the kali gandaki watershed area, nepal. J. Ethnopharmacol. 73,175-83.

Karimi, G., Aghasizadeh, M., Razavi, M., Taghiabadi, E., 2011. Protective effects of aqueous and ethanolic extracts of *Nigella sativa* L. and *Portulaca oleracea* L. on free radical induced hemolysis of RBCs. Daru 19,295-300.

Karimi, G., Hosseinzadeh, H., Ettehad, N., 2004. Evaluation of the gastric antiulcerogenic effects of *Portulaca oleracea* L. extracts in mice. Phytother. Res. 18, 484-487.

Karimi, G., Khoei, A., Omidi, A., Kalantari, M., Babaei, J., Taghiabadi, E., Razavi, B.M., 2010. Protective effect of aqueous and ethanolic extracts of *Portulaca oleracea* against cisplatin induced nephrotoxicity. Iran. J. Basic Med. Sci. 13, 31-35

Kim, J.A., Yang, S.Y., Kang, S., Kim, Y.H., 2012. Cyclooxgenase inhibitory components from *Portulaca oleracea*. Nat. Prod Sci. 18, 22-25.

Kishore, D., Moosavi, F., Varma, R., 2013. Effect of ethanolic extract of *Portulaca oleracea* Linn. On ethylene glycol and ammonium chloride induced urolithiasis. Int. J. Pharm. Pharm. Sci. 5, 134-140.

Kumar, A., Sharma, A., Vijayakumar, M., Rao Ch, V., 2010. Antiulcerogenic Effect Of Ethanolic Extract Of *Portulaca oleracea* Experimental Study. Pharmacol. Online 1, 417-432.

Lan, X., Dongming, X., Wei, W., Rufeng, W., Lijun, D., 2006. Review on chemical constituents of *Portulaca oleracea* L. Asia-Pa Trad. Med. 7, 035.

Lans, C.A., 2006. Ethnomedicines used in Trinidad and Tobago for urinary problems and diabetes mellitus. J. Ethnobiol. Ethnomed. 2, 45.

Lee, A.S., Kim, J.S., Lee, Y.J., Kang, D.G., Lee, H.S., 2012a. Anti-TNF-α activity of *Portulaca oleracea* in vascular endothelial cells. Int. J. Mol. Sci. 13, 5628-5644.

Lee, A.S., Lee, Y.J., Lee, S.M., Yoon, J.J., Kim, J.S., Kang, D.G., Lee, H.S., 2012. An aqueous extract of *Portulaca oleracea* ameliorates diabetic nephropathy through suppression of renal fibrosis and inflammation in diabetic db/db mice. Am. J. Chin. Med. 40, 495-510.

Lee, A.S., Lee, Y.J., Lee, S.M., Yoon, J.J., Kim, J.S., Kang, D.G., Lee, H.S., 2012b. *Portulaca oleracea* ameliorates diabetic vascular inflammation and endothelial dysfunction in db/db mice. Evid. Based Complement. Alternat. Med. 2012,741824.

Leung, W.K., Wu, J.C., Liang, S., Chan, L., Chan, F.K., Xie, H., Fung, S.S., Hui, A.J., Wong, V.W., Che, C.-T., 2006. Treatment of diarrhea-predominant irritable bowel syndrome with traditional Chinese herbal medicine: a randomized placebo-controlled trial. Am. J. Gastroenterol. 101, 1574-1580.

Lev, E., Amar, Z.. 2002. Ethnopharmacological survey of traditional drugs sold in the kingdom of jordan. J. Ethnopharmacol. 82,131-45.

Liang, X., Tian, J., Li, L., Gao, J., Zhang, Q., Gao, P., Song, S., 2014. Rapid determination of eight bioactive alkaloids in *Portulaca oleracea* L. by the optimal microwave extraction combined with positive-negative conversion multiple reaction monitor (+/-MRM) technology. Talanta 120, 167-172.

Liu, L., Howe, P., Zhou, Y.F., Xu, Z.Q., Hocart, C., Zhan, R., 2000. Fatty acids and beta-carotene in australian purslane (*Portulaca oleracea*) varieties. J. Chromatogr. A 893, 207-213.

Malek, F., Boskabady, M. H., Borushaki, M. T., & Tohidi, M. (2004). Bronchodilatory effect of Portulaca oleracea in airways of asthmatic patients. J. Ethnopharmacol., 93, 57-62.

Malzy P. 1954a. Aliments crus et masticatoires du nord cameroun. Journal d'agriculture tropicale et de botanique appliquée 1,441-452.

Malzy P. 1954b. Quelques plantes du nord cameroun et leurs utilisations. Journal d'agriculture tropicale et de botanique appliquée 1,148-179.

Masoodi, M.H., Ahmad, B., Mir, S.R., Zargar, B.A., Tabasum, N., 2011. *Portulaca oleracea* L. a review. J. Pharmacy Res. 4, 3044-3048.

Megaloudi F. 2005. Wild and cultivated vegetables, herbs and spices in greek antiquity (900 bc to 400 bc). Environ. Archaeol. 10,73-82.

Meng, Y., Ying, Z., Xiang, Z., Hao, D., Zhang, W., Zheng, Y., Gao, Y., Ying, X., 2016. The anti-inflammation and pharmacokinetics of a novel alkaloid from *Portulaca oleracea* L. J. Pharm. Pharmacol. 68, 397-405.

Miladi, G.H., Rashidipour, A., Ghorbani, R., 2005. Antinociceptive effects of the aqueous extracts of *Portulaca oleracea* seeds in mice. J. Babol U. Med. Sci. 7, 7-11.

Mosaddegh M, Naghibi F, Moazzeni H, Pirani A, Esmaeili S. 2012. Ethnobotanical survey of herbal remedies traditionally used in kohghiluyeh va boyer ahmad province of iran. J. Ethnopharmacol. 141,80-95.

Musa, K., Ahmed, A., Ibrahim, G., Ojonugwa, O., Bisalla, M., Musa, H., Danmalam, U., 2007. Toxicity studies on the methanolic extract of *Portulaca oleracea* L.(Fam. Portulacaceae). J. Biol. Sci. 7, 1293-1295.

Nadkarni, K.M., 1996. Dr. KM Nadkarni's Indian materia medica: with Ayurvedic, Unani-Tibbi, Siddha, allopathic, homeopathic, naturopathic & home remedies, appendices & indexes. 1. Popular Prakashan, Bombay.

Nayaka, H.B., Londonkar, R.L., 2014. Evaluation of *Portulaca oleracea* for anti-fertility effect in female albino rats. Int. J. Pharm. Pharm. Sci. 6,86-89.

Odhav, B., Thangaraj, K., Khumalo, N., Baijnath, H., 2013. Screening of African traditional vegetables for their alpha-amylase inhibitory effect. J. Med .Plant Res. 4, 1502-1507.

Oh, K.B., Chang, I.M., Hwang, K.J., Mar, W., 2000. Detection of antifungal activity in *Portulaca oleracea* by a single-cell bioassay system. Phytotherapy research 14, 329-332.

Osbaldeston, T.A., 2000. Dioscorides De Materia Medica. IBIDIS Press, Johannesburg, South Africa, pp.272-275.

Palaniswamy, U.R., McAvoy, R.J., Bible, B.B., 2001. Stage of harvest and polyunsaturated essential fatty acid concentrations in purslane (*Portulaca oleraceae*) leaves. J. Agric. Food Chem. 49, 3490-3493.

Parry, O., Marks, J.A., Okwuasaba, F.K., 1993. The skeletal muscle relaxant action of *Portulaca oleracea*: role of potassium ions. J. Ethnopharmacol. 40, 187-194.

Parry, O., Okwuasaba, F.K., Ejike, C., 1987. Skeletal muscle relaxant action of an aqueous extract of *Portulaca oleracea* in the rat. J. Ethnopharmacol. 19, 247-253.

Parvin, N., Farzaneh, S., Vardanjani, L.R., Goodarzi, I., Nikfarjam, M., 2013. 423–The effects of *Portulaca oleracea* L (purslane) on psychologic symptoms of schizophrenic patients. Eur. Psychiatry 28, 1.

Payudara, S., Dan Nasofarinks, K., Tan, G., Wong, K., PEArLE-WoNG, G.Q., Yeo, S., YEAP, S.K., YiAP, B.C., huEh, Z., 2013. In vitro Cytotoxic and antiproliferative effects of *Portulaca oleracea* methanol extract on breast, cervical, colon and nasopharyngeal cancerous cell lines. Sains Malays. 42, 927-935.

Pieroni, A., Dibra, B., Grishaj, G., Grishaj, I., Gjon Macai, S., 2005. Traditional phytotherapy of the Albanians of Lepushe, Northern Albanian Alps. Fitoterapia 76, 379-399.

Petropoulos, S., Karkanis, A., Martins, N., Ferreira I.C.F.R., 2016. Phytochemical composition and bioactive compounds of common purslane *(Portulaca oleracea* L.) as affected by crop management practices. Trends. Food Sci. Technol. 55,1-10.

Powell, O., Wilkins J., 2003. Galen: On the properties of foodstuffs. Cambridge University Press:103.

Quinlan, M.B., Quinlan, R.J., Nolan, J.M., 2002. Ethnophysiology and herbal treatments of intestinal worms in dominica, west indies. J. Ethnopharmacol. 80,75-83.

Radhakrishnan, R., Zakaria, M.N.M., Islam, M.W., Chen, H.B., Kamil, M., Chan, K., Al-Attas, A., 2001. Neuropharmacological actions of Portulaca oleraceae L v. sativa (Hawk). J.Ethnopharmacol. 76, 171-176.

Razi, M.Z., 1968. Al-Hawi fi'l-Tibb (Comprehensive Book of Medicine). Osmania Oriental Publications Bureau, Hyderabad.

Sabzghabaee, A.M., Kelishadi, R., Jelokhanian, H., Asgary, S., Ghannadi, A., Badri, S., 2014. Clinical effects of *Portulaca oleracea* seeds on dyslipidemia in obese adolescents: a triple-blinded randomized controlled trial. Med. Arch. 68, 195.

Sakai, N., Inada, K., Okamoto, M., Shizuri, Y., Fukuyama, Y., 1996. Portuloside A, a monoterpene glucoside, from *Portulaca oleracea*. Phytochemistry 42, 1625-1628.

Salehi, P., Asghari, B., Esmaeili, M.A., Dehghan, H., Ghazi, I., 2013. Glucosidase and amylase inhibitory effect and antioxidant activity of ten plant extracts traditionally used in Iran for diabetes. J. Med. Plant Res. 7, 257-266.

Samuelsson, G., Farah, M.H., Claeson, P., Hagos, M., Thulin, M., Hedberg, O., Warfa, A.M., Hassan, A.O., Elmi, A.H., Abdurahman, A.D., 1993. Inventory of plants used in traditional medicine in Somalia. IV. Plants of the families Passifloraceae-Zygophyllaceae. J. Ethnopharmacol. 38, 1-29.

Seo, Y., Shin, J., Cha, H.J., Kim, Y.-A., Ahn, J.-W., Lee, B.-J., Lee, D.S., 2003. A new monoterpene glucoside from *Portulaca oleracea*. Bull. Korean Chem. Soc. 24, 1475-1477.

Shabsoug, B., Khalil, R., Abuharfeil, N., 2008. Enhancement of natural killer cell activity in vitro against human tumor cells by some plants from Jordan. J. Immunotoxicol. 5, 279-285.

Sharma, A., Kaithwas, G., Vijayakumar, M., Unnikrishnan, M., Rao, C.V., 2012. Antihyperglycemic and antioxidant potential of polysaccharide fraction from *Portulaca oleracea* seeds against streptozotocin-induced diabetes in rats. J. Food Biochem. 36, 378-382.

Shirani, K., Hassani, F.V., Razavi-Azarkhiavi, K., Heidari, S., Zanjani, B.R., Karimi, G., 2015. Phytotrapy of cyclophosphamide-induced immunosuppression. Environ. Toxicol. Pharmacol. 39, 1262-1275.

Shobeiri, S.F., Sharei, S., Heidari, A., Kianbakht, S., 2009. *Portulaca oleracea* L. in the treatment of patients with abnormal uterine bleeding: a pilot clinical trial. Phytother. Res. 23, 1411-1414.

Simopoulos, A.P., 2004. The traditional diet of greece and cancer. Eur. J. Cancer Prev. 13,219-30.

Simopoulos, A.P., Tan, D.X., Manchester, L.C., Reiter, R.J., 2005. Purslane: a plant source of omega-3 fatty acids and melatonin. J. Pineal Res. 39, 331-332.

Tanji, A., Nassif, F., 1995. Edible weeds in morocco. Weed Technology, pp.617-620.

Tian, J.L., Liang, X., Gao, P.Y., Li, D.Q., Sun, Q., Li, L.Z., Song, S.J., 2014. Two new alkaloids from *Portulaca oleracea* and their cytotoxic activities. J. Asian Nat. Prod. Res. 16, 259-264.

Ullah, M., Khan, M.U., Mahmood, A., Malik, R.N., Hussain, M., Wazir, S.M., Daud, M., Shinwari, Z.K., 2013. An ethnobotanical survey of indigenous medicinal plants in wana district south waziristan agency, pakistan. J. Ethnopharmacol. 150,918-924.

Vahdati Hassani, F., Rezaee, R., Sazegara, H., Hashemzeai, M., Shirani, K., Karim, G., 2015. Effects of silymarin on neuropathic pain and formalininduced nociception in mice. Iran. J. Basic Med. Sci. 18,715-720.

Younos, C., Fleurentin, J., Notter, D., Mazars, G., Mortier, F., Pelt, J.M. 1987. Repertory of drugs and medicinal plants used in traditional medicine of afghanistan. J. Ethnopharmacol. 20,245-290.

Wainstein, J., Landau, Z., Dayan, Y.B., Jakubowicz, D., Grothe, T., Perrinjaquet-Moccetti, T., Boaz, M., 2016. Purslane extract and glucose homeostasis in adults with type 2 diabetes: a double-blind, placebo-controlled clinical trial of efficacy and safety. J. Med. Food 19, 133-140.

Wang, C.Q., Yang, G.Q., 2010. Betacyanins from *Portulaca oleracea* L. ameliorate cognition deficits and attenuate oxidative damage induced by D-galactose in the brains of senescent mice. Phytomedicine 17, 527-532.

Wang, W., Gu, L., Dong, L., Wang, X., Ling, C., Li, M., 2007. Protective effect of *Portulaca oleracea* extracts on hypoxic nerve tissue and its mechanism. Asia Pac. J. Clin. Nutr. 16, 227-233.

Wanyin, W., Liwei, D., Lin, J., Hailiang, X., Changquan, L., Min, L., 2012. Ethanol extract of *Portulaca oleracea* L. protects against hypoxia-induced neuro damage through modulating endogenous erythropoietin expression. J. Nutr. Biochem. 23, 385-391.

Xiang, L., Xing, D., Wang, W., Wang, R., Ding, Y., Du, L., 2005. Alkaloids from *Portulaca oleracea* L. Phytochemistry 66, 2595-2601.

Xiao, F., Lu, F., Xu, L., 2005. Effect of different parts of *Portulace oleracea* on the levels of TNF-alpha and IL-6 in the supernatant of cultured adipose cell. Zhongguo Zhong Yao Za Zhi 30, 1763-1766.

Xin, H.-L., Hou, Y.-H., Xu, Y.-F., Yue, X.-Q., Li, M., Lu, J.-C., Ling, C.-Q., 2008. Portulacerebroside A: New Cerebroside from *Portulaca oleracea* L. Chinese Journal of Natural Medicines 6, 401-403.

Xin, H.L., Xu, Y.F., Hou, Y.H., Zhang, Y.N., Yue, X.Q., Lu, J.C., Ling, C.Q., 2008. Two novel triterpenoids from *Portulaca oleracea* L. Helv. Chim. Acta 91, 2075-2080.

Xu, X., Yu, L., Chen, G., 2006. Determination of flavonoids in *Portulaca oleracea* L. by capillary electrophoresis with electrochemical detection. J. Pharm. Biomed. Anal. 41, 493-499.

Xu, Z., Shan, Y., 2014. Anti-fatigue effects of polysaccharides extracted from *Portulaca oleracea* L. in mice. Indian J. Biochem. Biophys. 51,321-325.

Yan, J., Sun, L.R., Zhou, Z.Y., Chen, Y.C., Zhang, W.M., Dai, H.F., Tan, J.W., 2012. Homoisoflavonoids from the medicinal plant *Portulaca oleracea*. Phytochemistry 80, 37-41.

Yang, Z., Liu, C., Xiang, L., Zheng, Y., 2009. Phenolic alkaloids as a new class of antioxidants in *Portulaca oleracea*. Phytother. Res. 23, 1032-1035.

Yao, D., Zhang, J., 1995. A coloured atlas of the Chinese materia medica specified in pharmacopoeia of the People's Republic of China. Guangdong Science and Technology Press, Guangdong, 57.

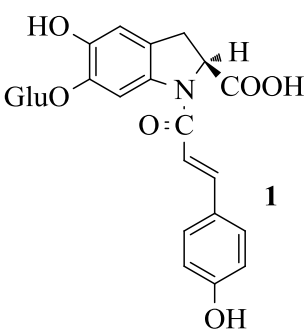
Yen, G.C., Chen, H.Y., Peng, H.H., 2001. Evaluation of the cytotoxicity, mutagenicity and antimutagenicity of emerging edible plants. Food Chem. Toxicol. 39, 1045-1053.

Yue, M.E., Jiang, T.F., Shi, Y.P., 2005. Simultaneous determination of noradrenaline and dopamine in *Portulaca oleracea* L. by capillary zone electrophoresis. J. Sep. Sci .28, 360-364.

Zakizadeh, E., Faghihimani, E., Saneei, P., Esmaillzadeh, A., 2015. The Effect of Purslane Seeds on Biomarkers of Oxidative Stress in Diabetic Patients: A Randomized Controlled Cross-over Clinical Trial. Int. J. Prev. Med. 6, 95.

Zhou, Y.-X., Xin, H.-L., Rahman, K., Wang, S.-J., Peng, C., Zhang, H., 2015. *Portulaca oleracea* L.: A review of phytochemistry and pharmacological effects. Biomed. Res. Int. 2015:925631.

Zhu, H. B., Wang, Y. Z., Liu Y. X., Xia, Y. l., Tang, T., 2010. Analysis of flavonoids in Portulaca oleracea L. by UV-vis spectrophotometry with comparative study on different extraction technologies. Food Anal. Methods 3, 90–97.



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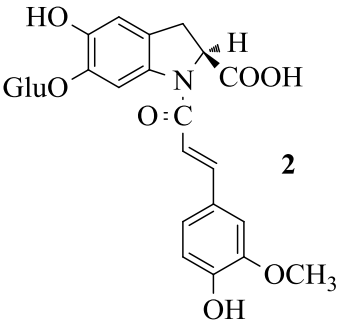

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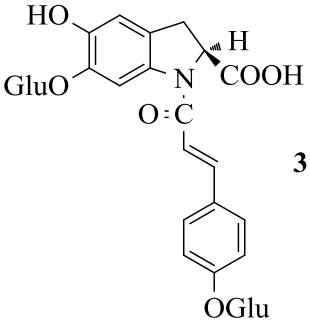

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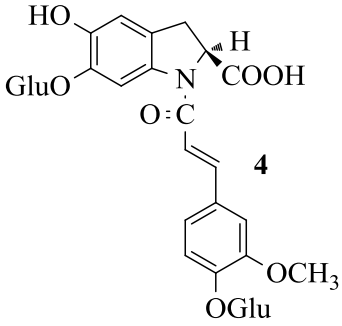

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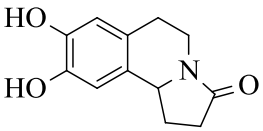

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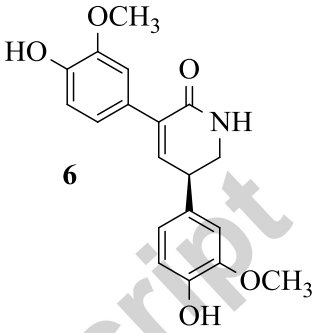

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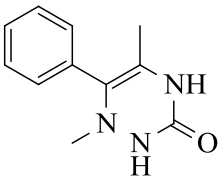

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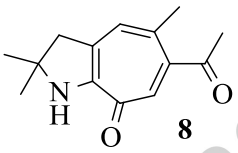

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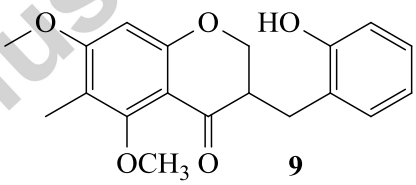

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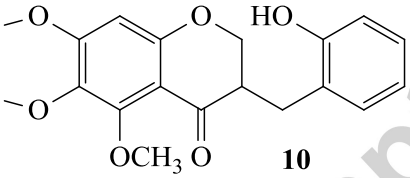

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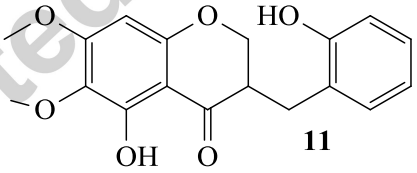

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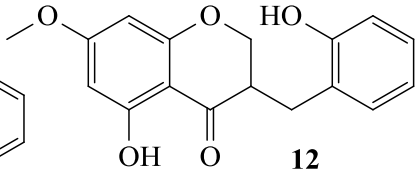

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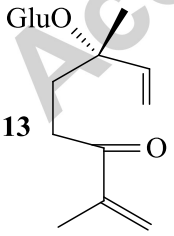

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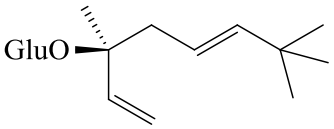

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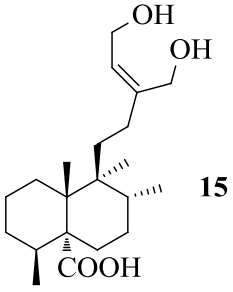

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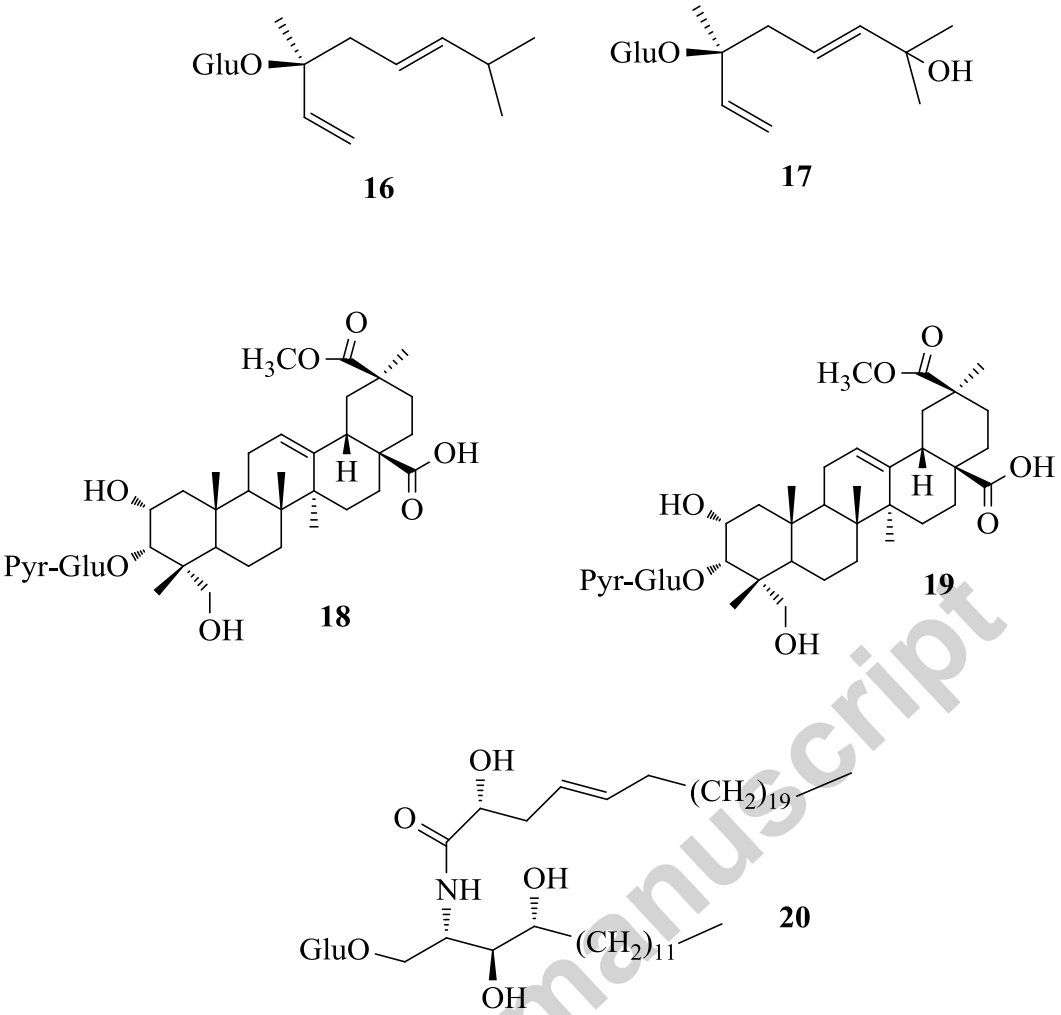

Figure 1. Chemical structures of novel secondary metabolites have been isolated from P. oleracea.

Table1. Ethnopharmacological uses of *P. oleracea* in different countries.

Country	Part used	Dosage form/Route of administration	Medicinal use/ disease treated	Reference(s)
Persia	Aerial parts, Seeds	Oral	hemoptysis, gastritis, liver inflammation, intestinal ulcers, kidneys and bladder ulcers, hemorrhagic vomiting, fevers, insomnia, cough, tonsillitis, asphyxia, nocturnal emissions.	(Aqili Khorasani, 2007; Aqili Khorasani, 1992; Razi, 1968; Jorjani., 1976 ; Ibn Sina, 1987; Amiri and

			As an anti-thirst, food digestive, anti-parasite, depurative, anti-hemorrhoids and diuretic medicine.	Joharchi, 2013; Ghasemi Pirbalouti et al., 2013; Mosaddegh et al., 2012)
	Aerial parts, seeds	External	severe inflammations, erysipelas, pulsatile headaches caused by hot temperament, eye pain, teeth sensitivity, blepharitis, mouth ulcers, testicular swelling	
	Roots	Poultice/ external	To eliminate warts	(Aqili Khorasani, 2007)
	seed's milky aqueous extract	Oral	Headaches, meningitis, encephalitis, thirst, melancholia, conjunctivitis, epistaxis, mouth ulcers, suffocation, tonsillitis, pleurisy, palpitation	Chashti, 1884)
China	Leaves	Oral	Dysentery with bloody stools, colitis, acute appendicitis, diabetes, bacterial infections, as a diuretic, cooling in fever, antitoxins	(Chen et al., 2009)
	Leaves	Poultice/external	Sores, eczema, erysipelas, dermatitis, shingles, snake- and insect-bite, pain and swelling, abnormal uterine bleeding, hemorrhoid bleeding, fever, tumors, ulcer, wounds	(Belcheff, 2012; Chen, J. et al., 2003; Yao and Zhang, 1995)
Nepal	leaves and seeds	Oral/external	For blood purification and to cure cardiovascular complaints, circulatory	(Joshi and Joshi, 2000)

			diseases, dental problems and toothache	
Philippines	Aerial parts	-	Wound healer, mild diuretic, anti-scorbutic, refrigerant	(Belcheff, 2012)
Albania	Aerial parts, fresh	External use on the legs/ oral	Anti-rheumatic, to cure musculoskeletal disorders and as a nutritional food	(Pieroni et al., 2005 ; Gonzalez-Tejero et al., 2008)
	Leaf juice	Drunk with milk and sugar	Anti-rheumatic	
Cyprus	Aerial parts	Oral	For alleviating mental disorders, musculoskeletal, CNS and cardiovascular diseases	(Della et al., 2006; Gonzalez-Tejero et al., 2008)
Spain	Seeds	Oral	Respiratory problems, cough, anorexia, spermatorrhea, hot fevers	(Al-Zahrawi, 2004; Carrio and Valles, 2012)
	Seeds	External	Aphtha, anosmia, hoarseness	
	Aerial parts	Oral	Cough, intestinal ulcers, polyuria, infertility caused by excessive heat, regulating blood pressure	
	Aerial parts	External	Headache, meningitis, epistaxis, aphasia, gout, arthralgia	
United Arab Emirates (UAE)	Aerial parts	-	Febrifuge	(El-Ghonemy, 1993)
Oman	Aerial parts	-	Febrifuge	(El-Ghonemy,

				1993)
Saudi Arabia	Aerial parts	Oral, topical	For the treatment of liver, gastrointestinal and inflammatory diseases	(Al-Asmari, 2014)
Jordan	seeds	Oral	as a blood purifier and an aphrodisiac	(Lev and Amar, 2002)
Egypt	Aerial parts, seeds	Oral	Curing hemoptysis, obsession, madness, bilious vomiting, inflammation of the stomach and liver, pain and stones of kidney and bladder, uterine and intestinal ulcers, nocturnal emissions, diabetes, worms, hypertension	(al-Nafis, 1999)
	Aerial parts, seeds	External/poultice	Headaches caused by heat, toothache, tooth numbness, epistaxis, hot fevers, inflammations, hemorrhoids, excessive heat in chest organs, excessive thirst, warts, urticaria, erysipelas, anthrax and to prevent gangrene	
Somalia	Whole plant	Oral, topical	Curing abdominal complaints, dysmenorrhoea, intestinal wounds, sinusitis, spastic paralysis, leprosy	(Samuelsson et al., 1993)
Nigeria			Muscular pains	(Parry et al., 1987)
west Africa	Juice and aqueous extract of the whole plant	External	Earache, toothache, swelling, boils and abscesses	(Habtemariam et al., 1993)

		Oral	Vermifuge, diuretic	
Benin	Leaves	-	Leprosy	(Bello et al., 2013)
North Cameroon	Aerial parts	Mastication	induce salivation	(Malzy, 1954a; Malzy, 1954b)
Ivory Coast	Grinded twigs and leaves	-	To facilitate childbirth	(Béné et al., 2016)
Morocco	Aerial parts	Oral	As an energizing food and salad and gastric tonic	(Bachar et al., 2016 ; Tanji and Nassif, 1995; Benkhnigue et al., 2010)
Greece	Aerial parts	Oral	Curing high cholesterol	(Albala, 2011)
	Aerial parts	Tea/ oral	curing sore throat, earache, diabetes, inflammations of the urinary system and high cholesterol level, Safe during pregnancy and lactation	(Simopoulos, 2004; Brussell, 2004 ; Megaloudi, 2005; Albala, 2011)
Italy	Aerial parts	Infusion, fresh leaves/ oral	Head and stomach illnesses, intestinal worms, urinary inflammations, lizard bites, diuretic, reddened gums, scurvy, analgesic for gastric, intestinal and kidney pain, haemorrhoids, haemoptysis, mouth and gum ulcers, toothaches, raspy voice. As a febrifuge, anaphrodisiac, detoxifying and	(Iserin et al., 2001; Guarrera and Savo, 2013; Guarrera, 2003; De Feo, 1992)

			emollient agent	
		Infusion/external	Skin rashes and pimples or boils	
	Leaves	Poultice	headaches, gastric acid, eye inflammations, gangrene prevention	
	Seeds and leaves	Infusion, oral	Dysentery and urogenital infections	(Bosi et al., 2009)
India	-	Oral	Diseases of the lungs, liver, kidneys, bladderand bowels, scurvy, asthma, leprosy, hemorrhoids, spitting of the blood and gastric inflammation and as a vegetable.	(Nadkarni, 1996; Anusha et al., 2011 ; Belcheff, 2012;
	-	External	Erysipelas, burns, scalds and various skin diseases	
Pakistan	fresh aerial parts/ juice	Oral/external	For the treatment of urinary and gastrointestinal problems (such as diarrhea and dysentery), swelling joints, burning sensation, coughs, earache, skin infections, sores and burns. PA is believed to be depurative, febrifuge and cardiac stimulant.	(Ullah et al., 2013; Abbasi et al., 2015).
	Seeds		demulcent, diuretic and vermifuge	
Afghanistan	seeds	Oral	As an antidiarrheal and for throat infection	(Younos et al., 1987)

Turkey	leaves	Oral	To cure diarrhea, diabetes, headache, ulcers, urinary disorders and wounds.	(Cakilcioglu and Turkoglu, 2010)
Australia	Aerial parts		Curing scurvy, alleviating irritations and inflammations and as a diuretic and antibiotic	(Belcheff, 2012)
America	Aerial parts		Curing cold, gout, headache, stomachache, excessive menstrual flow, cough	(Belcheff, 2012 ; Chapman et al., 1973; Liu et al., 2000)
	Leaves	Juice	Inflammation of the male genitalia, as a vegetable	
	Aerial parts	Poultice	Burns	
	Leaves	Infusion/liniment	Stiff neck	
		Decoction	Gonorrhea	
	Seeds	Boiled	Curing worms	
Dominica	-	Oral	intestinal worms	(Quinlan et al., 2003)
Trinidad and Tobago	Aerial parts	Oral	High blood cholesterol, shortness of breath	(Lans, 2006)
Columbia	-	External	As an emollient, to cure tumors, callosities	(Belcheff, 2012)

Table 2. Main secondary metabolites have been isolated from P. oleracea. The numbers in the parenthesis refer to the chemical structures presented in figure 1.

Class of compounds	Chemical compound	Part of plant	Reference(s)
Alkaloids	Oleracein A (1)	Whole plant	(Xiang et al.,

	Oleracein B (2)		2005)
	Oleracein C (3)		
	Oleracein D (4)		
	Oleracein E (5)		
	Oleracins I	Stems	
	Oleracins II	Stems	
	(3*R*)-3,5-bis(3-methoxy-4-hydroxyphenyl)-2,3-dihydro-2(1*H*)-pyridinone (6)	Aerial parts	(Tian et al., 2014)
	1,5-dimethyl-6-phenyl-1,2-dihydro-1,2,4-triazin-3(2*H*)-one (7)	Aerial parts	
	Oleracone (8)	Whole plant	(Liang et al.,
	Trollisine	Aerial parts	2014)
	Aurantiamide acetate		
	Aurantiamide		
	Scopoletin		
	Dopamine	Stems, leaves and seeds	(Yue et al., 2005)
	Noradrenalin	Stems, leaves and seeds	(Chen, Juan et al., 2003)
Flavonoids	Portulacanones A (9)	Aerial parts	(Yan et al.,
	Portulacanones B (10)		2012)
	Portulacanones C (11)		
	Portulacanones D (12)		
	Kaempferol	Whole plant	(Xu et al.,

	Apigenin		2006)
	Luteolin		
	Myricetin		
	Quercetin		
Terpenoids	Portuloside A (13)	Aerial parts	(Sakai et al., 1996)
	Portuloside B (14)		(Seo et al., 2003)
	Portulene (15)		(Elkhayat, et al., 2008)
	Lupeol		
	(3S)-3-O-(*β*-D-Glucopyranosyl)-3,7-dimethylocta-1,6-dien-3-ol (16)		(Seo et al., 2003)
	(3S)-3-O-(*β*-D-Glucopyranosyl)-3,7-dimethylocta-1,5-dien-3,7-diol (17)		(Seo et al., 2003)
	(2α,3α)-3-{[4-O-(*β*-D-Glucopyranosyl)-*β*-D-xylopyranosyl]oxy}-2,23-dihydroxy-30-methoxy-30-oxoolean-12-en-28-oic acid (18)		(Xin, H.L. et al., 2008)
	(2α,3α)-2,23,30-Trihydroxy-3-[(*β*-D-xylopyranosyl)oxy]olean-12-en-28-oic acid (19)		(Xin, H.L. et al., 2008)
	Friedelane		(Xin, H.L. et al., 2008)
Organic	a-Linolenic acid	Leaves	(Simopoulos

acids	Palmitic acid	Leaves	et al., 2005)
	Stearic acid	Leaves	(Palaniswamy et al., 2001)
	Oleic acid		
	Linolenic acid		
Other compounds	Portulacerebroside A (20)	Aerial parts	(Xin, H.-L. et al., 2008)
	Melatonin	Leaves	(Simopoulos et al., 2005)

Table 3. Summary of pharmacological activities of *Portulaca oleracea*

Activity	Dosage form/ type of extract	Effective concentrations/ dosages/ route of administration	Model	Tested living system/ organ/cell	Result	References
Renoprotective activity	Aqueous extract	400 mg/kg, p. o.	Gentamicin-induced nephrotoxicity	Rats	Decreased plasma levels of urea, uric acid and creatinine	(Hozayen et al., 2011)
	Aqueous	0.2, 0.4	Cisplatin-	Rats	Decreased BUN	(Kari

	and ethanolic extracts	and 0.8 g/kg. i.p./ 0.5, 1 and 2 g/kg, i.p.	induced nephrotoxicity		and creatinine levels	mi et al., 2010)
	Aqueous extract	300 mg/kg/day, p.o.	Diabetic nephropathy	Mice	Decreased diabetic nephropathy by inhibition of renal fibrosis and inflammation/ suppressed NF-β p65 activation	(Lee, A. S. et al., 2012)
	Ethanolic extract	100, 200 and 400 mg/kg/day for 15 days, p.o.	ethylene glycol and ammonium chloride induced calcium oxalate uroliths	Rat	Antiurolithiatic activity	(Kishore et al., 2013)
Neuroactivity	Not defined	The end concentrations of the PO extract were 0%, 5%, 10%, 20%	Hypoxia	PC-12 cells	Increased the cell viability under hypoxia conditions	(Wang et al., 2007)
	Not defined	1 g/day. p. o.	Hypoxia	BALB/c mice	increased the level of ATP, lactate dehydrogenase (LDH), phosphofructokinase (PFK) and pyruvate kinase (PK) of hypoxic brain cortices/increased erythropoietin mRNA expression	
	Ethanolic extract	2 mg/kg, p. o.	Hypoxia	mice	Stimulated erythropoietin expression at both mRNA and protein levels/ decreased the	(Wanyin et al., 2012)

					enolase levels and the activity of caspase-3	
	Aqueous extract	1.5 mL/kg, p. o.	Rotenone-induced brain damage	Rat	inhibited dopamine metabolism and apoptosis induction in the striatum	(Abdel Moneim, 2013)
	Aqueous extract	2.5 to 10 mg/kg/day, s. c.	D-galactose induced neurotoxicity	Mice	Reversed reductions in crossing, rearing/leaning and grooming activities	(Hongxing et al., 2007)
	Aqueous extract	1.5 mL/kg, p.o.	Effect on neurotransmitters	Rat	Increased levels of serotonin, norepinephrine dopamine and acetyl cholinesterase in some parts of the brain	(Moneim et al., 2012)
	polysaccharides	100, 200 and 400 mg/kg p. o.	Forced swimming test	Mice	Increase the swimming time to fatigue of the mice	(Xu and Shan, 2014)
	Ethanolic extract	200 mg/kg, i. p.	Pentylenetetrazole-induced convulsion	Mice	increase on the onset time of	(Chan, K et al., 2000)
	Dried ethanolic extract	1 g/day, p.o.	Clinical trial	Schizophrenic patients	Reduced the mean score of positive and negative symptoms	(Parvin et al., 2013)
Muscle relaxant effects	Aqueous extract	200-1000 mg/kg, i.p.	Pull- up test	Rats	Reduced pull-up time	(Parry et al., 1993)
Metabolic effects	Proteinous compounds of the aqueous extract	77.5 mg/kg, i.p.		Mice	Decrease serum glucose, cholesterol, triglycerides and total lipids as well as glycogen level in liver	(AL–Chalabi)
	Purslane/pumpkin seed	2 g/100 g diet	Hypercholesterolemic	Rats	has hypolipidemic,	(Barakat

	mixture				hypotriglyceridemic and hypocholesterolemic	and Mahmoud, 2011)
	Aqueous extract	300 mg/kg/day, p.o.	Diabetic	db/db mice	prevented the development of diabetic endothelial dysfunction	(Lee, An Sook et al., 2012b)
	Seeds	500 mg, twice a day	Clinical trial	Dyslipidemic patients	Significantly reduced LDL-C and TG levels	(Sabzghabaee et al., 2014)
	Seeds	5g, p.o.	Clinical trial	Type 2 diabetes mellitus	Notable hypoglycaemic, hypolipidaemic and insulin resistance reducer effects	(El-Sayed, 2011)
Hepatoprotective effects	Aqueous ethanol (80% v/v)	0.01, 0.05, 0.1, and 0.15 g/kg	CCl_4-induced hepatotoxicity	Rats	restoring the levels of serum enzymes to normal	(Eidi et al., 2015)
Abnormal uterine bleeding (AUB)	seeds	5 g	Clinical trial	Premenopausal women with AUB	The volume and duration of bleeding had reduced	(Shobeiri et al., 2009)