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Pharmacological potentials of phenolic compounds from *Prosopis* spp.-a review

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ABSTRACT

The shrub *Prosopsis juliflora* (Sw.) DC. revealed several medicinal properties due to its different chemical compounds such as alkaloids, flavonoids, terpenoids, saponins and phenolic compounds distributed in different parts of the plant body, such as woody parts (roots, stem, branches and bark) as well as leaves and pollen have been used for the extraction of medically active substances. *Prosopsis juliflora* containing a diverse group of secondary metabolites has unique and multifactorial medicinal properties. The utilization of this abundant resource provides a viable option for producing bioactive natural products that may serve as lead substances for the chemical and pharmaceutical industries. This review highlights accessible bioactive sources from this plant that are of potential interest for industrial applications.

1. Introduction

Despite the progress in conventional chemistry and pharmacology in the production of effective drugs, plants might provide a useful source of new medicines and may be used to replace existing drugs[1]. Traditional medicine in general is turned out to be very useful in the discovery of natural products such as pharmaceutical drugs[2]. The shrub *Prosopsis juliflora* (Sw.) DC. (*P. juliflora*) (Figure 1) commonly known as mesquite has been used as a traditional medicine on different continents for curing catarrh, colds, diarrhea, dysentery, excrescences, flu, hoarseness, inflammation, measles, sore throat, and for the healing of wounds[3]. This review evaluates the pharmacological potential with emphasis on naturally occurring phenolic compounds from *P. juliflora*.

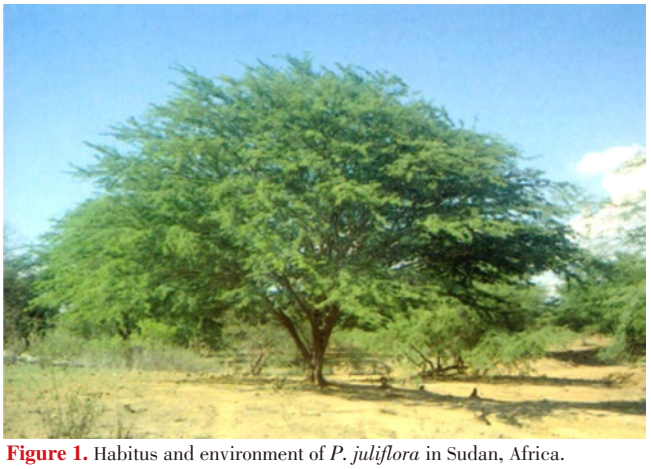

Figure 1. Habitus and environment of *P. juliflora* in Sudan, Africa.

2. Botanical description

The genus *Prosopis* comprises 44 species with 40 native to the Americas. *Prosopis africana* (Guill. & Perr.) Taub.

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(*P. africana*) is indigenous to Africa, whereas *Prosopis kodziana*, *Prosopis farcta* (Banks & Saland.) J. F. Macbr. (*P. farcta*) and *Prosopis cineraria* (L.) Druce (*P. cineraria*) are native to the Middle East and Pakistan[4]. The placing of *Prosopis* spp. in a wider taxonomic classification system was based on Lewis and Elias[5]. *Prosopis* spp. grow in a wide array of environments and are commonly not restricted by soil type, pH or salinity. They grow in semi-arid and arid tracts of tropical and sub-tropical regions of the world and are spreading fast because the leaves are unpalatable and animals do not digest its seeds[6]. In India this species has been found to be of great value for the rehabilitation of saline and alkaline soils especially in the northern parts of the country[7,8]. Apart from poor soils, *Prosopis* trees withstand exceptionally high temperatures (45 °C) in summer and cool temperatures in winter[9].

Although *P. juliflora* is a potential source of fuel wood, timber, providing pods for animal forage and its flowers as a source for honey-producing bees, it became a rather competitive weed and it has been declared as a noxious weed in several countries[10]. Invasions by *Prosopis* spp. to grasslands, protected forests and nature reserves provided alarming signals. These trees dry out soil and compete with grasses, particularly in dry areas and it is therefore considered as a weed in many areas[11].

In the last 200 years, species of *Prosopis* have been introduced or reintroduced to certain areas of Argentina, Chile, Peru, Mexico and the USA as well as to some regions of Asia, Africa, India and Australia[12]. The majority of introduced species were belonging to *P. juliflora*, *Prosopis pallida* (Humb. & Bonpl. ex Willd.) Kunth., *Prosopis glandulosa* Torr. and *Prosopis velutina* Wooton. The former two species are prevalent in the tropics, while the latter two are found in more sub-tropical areas. Species like *Prosopis alba* Griseb. (*P. alba*) and *Prosopis chilensis* (Molina) Stuntz. (*P. chilensis*) are proven to be well adapted and are locally common in some regions[12]. *P. juliflora* wood has been described as a source of lumber, firewood, activated carbon and charcoal. There is a considerable potential for *P. juliflora* as a source of fiber for paper, paperboard and hardboard industries[8,13]. Drought tolerant genes were identified from *P. juliflora* through analyses of expressed sequence tags. It has been presently used as a source of drought tolerant genes for transgenic crop plants[14].

3. Chemical composition

The constituents of woody biomass can be divided into cellulose, hemi-cellulose, lignin, extractives, ash and water. The levels of chemical constituents in *P. juliflora* have been estimated as 25%-30% hemicellulose, 40%-45% cellulose, 11%-28% lignin and 3%-15% extractives[15]. Extractive chemicals from woody biomass include sugar, resins, volatile oils, fatty acids, tannins, alcohols and phenols with a tannin content of up to 9% of the woody material (Table 1 and Figure 2). The heartwood of different *Prosopis* spp. contains significant amounts of wood extracts and polyphenol compounds[16]. Juliflorine, the main alkaloid of *P. juliflora* was isolated and its partial structure was reported by Ahmad *et al.*[17]. Later, Longoni *et al.*[18] reported the complete structure of juliflorine (juliprosopine) from *P. juliflora*. Juliflorine has been reported to possess antidermatophytic[19] and antibacterial activities[20].

Table 1

Bioactive compounds from *Prosopis* spp.

Species	Parts used	Metabolite/compound	Effect	References
P. juliflora (Sw.) DC.	–	Juliflorine	Antidermatophytic	[19]
	Leaves	–	Hemolytic	[57]
		Alkaloids	Antifungal	[20,38,58]
			Antibacterial	[20,24,57]
			Anti-inflammatory	[58]
			Cytotoxicity	[42,59]
			Antitumoral activity	[42]
		Juliflorine, julifloricine	Antimicrobial activity	[40]
		3′-oxo-juliprosopine, sceojuliprosopinol, 3-oxojuliprosine, 3′-oxo-juliprosine	Growth inhibitory activity	[60]
	Bark	Quercetin 4′,7-dimethylether, kaempferol 4′-O-methyether, retusin, L-manopyranoside	Antifungal activity	[32]
	Pods	Alkaloids	Cytotoxicity	[61]
	–	Juliflorine	Inhibitor of acetylcholinesterase and butyrylcholinesterase enzymes	[43]
	Pollens	Flavonols	Antioxidant effect	[44]
	Leaves	Julifloravizole	Antifungal	[62]
	Leaves	Alkaloids, flavonoids, phenols	Antibacterial	[63]
	Heart wood	Mesquitol	Antioxidant	[27]
	Barks	3′-oxo-juliprosopine, secojuliprosopinol	Anti-inflammatory	[42]
	Leaves	–	Antihyperlipidemic	[1]
P. alba Griseb.	Leaves	Catechin	Antioxidant	[34]
P. chilensis (Molina) Stuntz and *P. tanarugo* Phil.	Leaves	Polyphenols	Antioxidant	[34]
Prosopis sp.	Aerial parts	5-Hydroxytryptamine	Antidepressant activity	[10]
		Apigenin	Antibacterial, antidermatitic, anti-inflammatory and antiviral activity	
		Isorhamnetin-3-diglucoside	Hepatoprotective activity	
		L-arabinose	No activity reported	
		Quercetin	Analgesic, antiallergenic, antibacterial, antidiabetic, anti-inflammatory and antiviral activity	
		Tryptamine	Antiamebic activity	
	Bark	Tannin	Antibacterial, antidiarrheic and antiviral activity	
P. africana (Guill. & Perr.) Taub.	Stem bark	Flavonoids	Anti-inflammatory activity	[45]

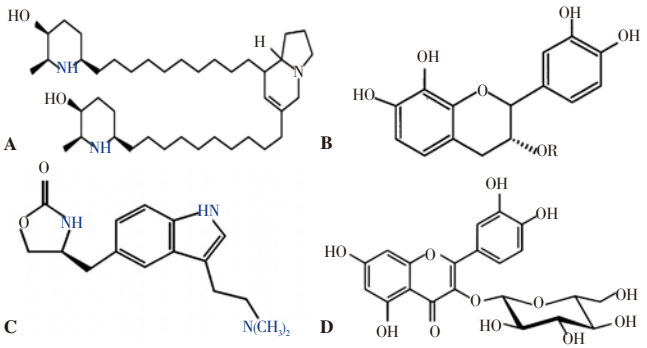

Figure 2. Molecular structure of bioactive compounds of *P. juliflora*. A: Juliflorine; B: Mesquitol; C: 5-Hydroxytryptamine; D: Isorhamnetin-3-diglucoside.

Leaves of *P. juliflora* contain alkaloids such as tryptamine, piperidine, phenethylamine and juliprosopine which have antifungal and plant growth inhibiting properties, and might induce neuronal damages in animals[21]. Mazzuca *et al.*[22] reported that the seeds of *Prosopis alpataco* exhibited antibacterial and antifungal activities while extracts of *Prosopis denudans* var. *denudans* and *Prosopis denudans* var. *patagonica* showed antifungal activities. Fatty acids and a group of pentacyclic triterpenes were identified as responsible compounds for antibacterial activities. Leaf extractives analyzed by gas chromatography-mass spectrometer showed the presence of physiologically relevant fatty acids such as hexadecanoic, octadecanoic acids, glucopyranose, hydroquinone, glucopyranosides and galactose sugars[23].

Prosopis spp. contain harman, prosopine, tyramine and prosopinine which are alkaloids that can intercalate with DNA[24]. Also, *Prosopis* spp. have caffeic acid derivatives[25] with antibiotic activities against viruses, bacteria and fungi[26]. They also contain quercetin 3-o-glucoside and quercetin 3-o-galactoside[25] which bind with extracellular and soluble proteins and complexes to bacterial cell walls.

Sirmah[23] identified epicatechin, catechin, gallocatechins, methylgallo-catechins, fatty acids and free sugars from *P. juliflora* bark, whereas the pods contain an important quantity of galactomannans, mannoses, saturated and unsaturated fatty acids and free sugars which are used as a food supplement and medicine for animals and humans. A large amount of flavonoid (-)-mesquitol has been extracted and isolated from the heartwood of *P. juliflora*. The product was able to slow down the oxidation of methyl linoleate induced by 2, 2′-azobis 2-methylpropionitrile[27].

4. *Prosopis* in traditional medicine

Phenolic compounds comprise one of the largest and the most ubiquitous groups of plant metabolites. They are synthesized to protect the plant from photosynthetic stress, reactive oxygen species, wounds, infections and herbivores. Phenolic compounds seem to be universally distributed in plants and they have been the subject of a great number of chemical, biological, agricultural and medical studies[28].

Many plants of the genus *Prosopis* are known to have medicinal properties and are used in traditional medicine as astringents, in rheumatism and as remedies against scorpion stings and snake bites[29]. The powdered flowers mixed with sugar are eaten by women during pregnancy as a safeguard against miscarriage[30]. There are also reports about the utilization of *Prosopis* spp. as a diuretic and for treating hepatic and ocular problems[31].

P. juliflora was used in Guatemala for the treatment of gonorrhea. They appeared most active against *Neisseria gonorrhea* (Neisser, 1879) isolates from symptomatic patients[32]. Stich[33] reported that *P. chilensis* (Molina) Stuntz. and *Prosopis tamarugo* Phil. (*P. tamarugo*) leaf extract and the exudate of *P. alba* Griseb. were active as free radical scavengers in the DPPH test. The free radical scavenging effect of *Prosopis* extracts was mainly due to compounds other than alkaloids[34].

In Mali, the leaves, bark, twigs and roots of *P. africana* are used to treat and relieve bronchitis, dermatitis, tooth decay, dysentery, malaria and stomach cramps. In Ghana, boiled roots are used for sore throat, root decoction for toothache and bark for healing wounds or cuts[35]. The extraction of *P. farcta* (Sol. ex Russell) J. F. Macbr. plant for treatment of angina pectoris in the Ilam Province of Iran in its long history of traditional medicine was reported. Also, the decoction of *P. farcta* plant has been used traditionally to reduce cardiac or chest pain in this province[36].

A review on the herbal traditional potential of *P. cineraria* from the Thar Desert is provided by Garg *et al.*[31]. *P. cineraria* is used traditionally for treatment of various ailments like leprosy, dysentery, asthma, leucoderma, dyspepsia and earache *etc*. Various phytoconstituents like tannins (gallic acid), steroids (stigmasterol, campesterol, sitosterol *etc.*), flavone derivatives (prosogerin A, B, C, D, and E), alkaloids (spicigerine, prosophylline) *etc.* has been isolated from the plant. Pharmacological activities like analgesic, antipyretic, antihyperglycemic, antioxidant, antihypercholesterolemic, antitumor, nootropic have been reported from different plant extracts.

5. Pharmacological potential of *P. juliflora*

Isolation and structural determination of two new alkaloids, juliprosinene and juliflorinine, from *P. juliflora* showed better antibacterial activity against strains of *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus* and *Shigella sonnei* (Table 1)[37]. The antimicrobial activity of benzene insoluble alkaloid mixture of the leaves of *P. juliflora* was measured *in vitro* and was found more effective than bacitracin, gentamycin,

chloromycetin and trimethoprim against *Staphylococcus aureus, Staphylococcus lactis, Staphylococcus faecalis, Staphylococcus pyogenes* and *Corynebacterium diphtheria*[24].

The extract of *P. juliflora* leaves showed better antibacterial activity against three phytopathogenic *Xanthomonas* pathovars *viz., Xanthomonas axonopodis* cf. *malvacearum, Xanthomonas axonopodis* cf. *phaseoli* and *Xanthomonas campestris* cf. *vesicatoria* associated with angular leaf spot of cotton, common blight of bean and bacterial spot of tomato, respectively, as well as 14 human pathogenic bacteria[38]. Furthermore, Aqeel *et al.*[39] investigated the antidermatophytic activity of juliflorine and a benzene insoluble alkaloidal fraction obtained from *P. juliflora* against *Trichophyton mentagrophytes* infection in rabbits. A tropical application of 2.5% juliflorine was found to heal 75% of dermatophytic lesions in three weeks.

Juliflorine possesses some immuno-modulating activity and this activity was tested in rabbits and compared with Freund's complete adjuvant in which *Listeria* hemolysin (antigen) was injected intramuscularly along with different concentrations of juliflorine with the result of a dose related immune response. After four weeks of weekly applications of 30 mg/kg of juliflorine, the antihemolysin titre was found to be higher (1:1 280) than that of Freund's complete adjuvant[40]. Batatinha[41] reported cytotoxic and antitumoral activity against human epithelial tumour cells (HeLa), human hepatic tumour (HepG2), and two fibroblast lineages F26 and F57 in *P. juliflora* extract.

The biological activity of the leaves and pods of *P. chilensis* and *P. tamarugo* was determined for free radical scavenging activity. The results suggest that the activity is related to polyphenols. The alkaloids β-phenethylamine and tryptamine were isolated from *P. chilensis*, and phenethylamine was detected in *P. tamarugo*. The activity was related to the total phenolic content which consisted mainly of catechin[34].

The methanolic extract of *P. juliflora* bark at 100, 200 and 400 mg/kg exhibited significant anti-inflammatory activity in acute and chronic inflammatory models. All the doses of methanolic extract of *P. juliflora* bark showed a dose dependent inhibition against histamine and serotonin induced rat paw oedema as compared with control animals. Furthermore, the same dose levels successfully reduced the formation of granulation tissues by cotton pellets in rats[42].

Tapia *et al.*[21] demonstrated bioactivity of the alkaloids tryptamine, phenethylamine and piperidine derivatives isolated from the extracts of aerial parts of *Prosopis alpataco, Prosopis argentina, P. chilensis* (Molina) Stuntz., *Prosopis flexuosa* DC. and *Prosopis pugionata*. The isolated compounds were assessed for DNA binding, β-glucosidase inhibition and free radical scavenging effects using the DPPH decoloration assay. At a concentration of 0.5 mg/mL of tryptamine, phenethylamine and piperidine derivatives, DNA binding activities showed the following ranges: tryptamine (28%), phenethylamine (0%-27%), piperidine derivatives (47%-54%). Tryptamine and 2-β-methyl-3-β-hydroxy-6-β-piperidinedo-decanol showed a moderate inhibition (27%-32%) of the enzyme β-glucosidase at 100 μg/mL. The exudate of *Prosopis flexuosa* which has the active constituent catechin displayed a strong free radical scavenging activity in a DPPH decolouration assay[21]. Choudhary *et al.*[43] reported the presence of acetylcholinesterase inhibitory substances in juliflorine from *Prosopis juliflora*.

Almaraz *et al.*[44] showed that pollen of *P. juliflora* provided an important source of flavonoids, which can be considered as natural antioxidants. Mesquite pollen extracts showed antioxidant activity related to the flavonoid concentration in both *in vitro* and *in vivo* systems, with a lower activity in the latter of these systems. Under *in vivo* conditions and in those where a state of oxidation is not induced, a high concentration of flavonoids in the extract of mesquite pollen can have a pro-oxidant effect.

Ayanwuyi *et al.*[45] reported an oral median lethal dose of the methanolic extract of *P. africana* at 3.808 g/kg in mice and >5 g/kg in rats and the study results support the traditional claim of the use of *P. africana* for the analgesic and anti-inflammatory activities. The effect of *P. farcta* plant extract showed a dose dependent as well as an endothelium dependent relaxing effect on the thoracic aorta in rats[36].

Antioxidant properties of heartwood of *P. juliflora* extract were estimated using a methyl linoleate oxidation inhibition test, showing that (-)-mesquitol, like (+)-catechin, was able to slow down oxidation of methyl linoleate induced by 2,2′-azobisisobutyronitrile. In both cases, the extract having flavanols showed higher antioxidant properties compared to butylated hydroxytoluene, which was chosen as the reference antioxidant[27]. Indeed, mesquitol in comparison with existing antioxidants such as probucol and alpha-tocopherol showed better antioxidant activity, which, therefore, can be useful in controlling inflammatory diseases, cancer and diabetes[46].

Ravikumar *et al.*[47] studied *in vitro* antiplasmodial activity of ethanolic extracts of South Indian medicinal plants against *Plasmodium falciparum* and found that leaf, bark and flower extracts of *P. juliflora* showed IC_{50} values of more than 100 μg/mL. Statistical analysis reveals significant antiplasmodial activity ($P<0.01$) between the concentrations and time of exposure. Additionally, no chemical injury was found in the erythrocytes incubated with the ethanolic extract of all the tested plants. The *in vitro* antiplasmodial activity might be due to the presence of alkaloids, glycosides, carbohydrates, flavonoids, phenols, saponins, triterpenoids, proteins and tannins in the ethanolic extracts of the tested plants.

6. Nutraceutical potential of *Prosopis*

García-Andradea *et al.*[48] found that mesquite leaves [*Prosopis laevigata* (Humb. & Bonpl. ex Willd.) M.C.Johnst.)] provide a natural resource with antioxidant capacity and cardioprotection potential. Purified fractions showed antihypertensive effects inhibiting angiotensin converting enzyme and cardioprotection inhibiting low density lipoprotein oxidation. The high performance liquid chromatography profile displayed phenolic compounds such as gallic acid, catechin, gallocatechin, epicatechin gallate, rutin, and luteolin that may explain these antioxidant and biological properties. Mesquite leaves can be a source of bioactive phenolics as nutraceutical ingredients.

Under environmental stress conditions, mesquite trees can excrete a proteinaceous arabinogalactan gum that is similar to gum arabic. Yolanda *et al.*[49] classified approximately 17.5% as top-quality gum. It was found that this class of mesquite gum has lower humidity, inorganic and tannins content than the other classes, or even than the gum arabic sample used as a reference. All of the mesquite gum classes have higher protein content and lower intrinsic viscosity than gum arabic.

Alftren *et al.*[50] compared the molecular and emulsifying properties of gum arabic and mesquite gum using asymmetric flow field-flow fractionation. They found that the protein content increased with increasing molar mass for both gums. Selective adsorption, during emulsification experiments, could be observed in population 2 of gum arabic which may be due to a combination of the higher protein content and a more flexible structure rendering it more surface active than population 1. Comparing gum arabic and mesquite gum in terms of emulsion stability, it could be concluded that gum arabic-stabilized emulsions have considerably higher stability against coalescence. Color and chemical stability of spray-dried blueberry extract was found the minimal when using mesquite gum as wall material[51]. The authors also found that microencapsulates being stored for 4 weeks at 4-8 °C at dark presented low degradation of phenolics (10%), anthocyanins (7%) and antioxidant activity (15%).

Prosopis flour might be capable of retaining a significant amount of antioxidant capacity after heating[52]. *Prosopis* extracts did not show any mutagenic effect with and without metabolic activation. *Prosopis* flour is proved to be a non conventional, novel and rich source of antioxidant compounds that could help to prevent pathologies associated with oxidative stress[52].

As for the improvement of feedstocks, Gupta *et al.*[53] found that irrespective of the substrates used, the chlorite treated substrates were enzymatically saccharified from 86.4% to 92.5% (w/w). The alkali treated substrates, however, containing 66%-76% (w/w) holocellulose could be enzymatically saccharified up to 55% (w/w). The acid pretreated substrates were found to contain almost 54%-62% (w/w) holocellulose, which on enzymatic hydrolysis could result in 39.5%-48.0% (w/w) saccharification.

Lopez-Franco *et al.*[54] characterized physicochemical and functional properties of galactomannans from mesquite seeds (*Prosopis* spp.). The sugars detected in their study were mannose and galactose, with a mannose: galactose ratio of 1.50. The curves obtained by calorimetry indicated a transition temperature, melting temperature and heat capacity very similar to those of the guar galactomannans. The evaluation of the functional properties of the mesquite galactomannans revealed a solubility of 92.10%, an emulsion capacity of 95% and an emulsion stability of 92.24%. The polysaccharide extracted from the mesquite seeds is a galactomannans with physicochemical and functional properties similar to those reported for other legume seed gums, allowing us to conclude that mesquite galactomannans has the potential for use in the food industry. Cardozo *et al.*[52]evaluated the antioxidant capacity, genotoxicity and polyphenol content of non-conventional foods *Prosopis* flour and found a high capacity.

7. Other potentials of *Prosopis*

For the bioethanol production from lignocellulosic biomass, it is required to remove lignin and increase the porosity of the substrate for saccharification. Naseeruddin *et al.*[55] selected the best chemical pretreatment for lignocellulosic substrate of *P. juliflora*. Among all the chemicals investigated, pretreatment with sodium dithionite at concentration of 2% (w/v) removed maximum lignin (80.46%±1.35%) with a minimum sugar loss (2.560%± 0.021%). Subsequent biphasic acid hydrolysis of the sodium dithionite pretreated substrate hydrolyzed (40.09±1.22)% of holocellulose and released minimum amount of phenolics [(1.040±0.022) g/L] and furans [(0.410±0.012) g/L] in the hydrolysate.

Pizzoa *et al.*[56] studied several types of extractives with five native argentine wood species of the genus *Prosopis*. The authors observed similarities implying that the various methods of extraction did not really extract only a single class of substances, and great care must be adopted when using some specific procedures for extractions. Furthermore, the existing relationships between extractives and selected technological properties, namely, the specific volumetric shrinkage coefficient (BSvol) and natural durability (evaluated in terms of mass loss after fungal attacks in laboratory conditions), were given.

Conflict of interest statement

We declare that we have no conflict of interest.

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