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Overview of Genus *Prosopis* Toxicity Reports and its Beneficial Biomedical Properties

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Abstract

Secondary plant metabolites are regarded as promising sources of plant-protecting substances and they are one of the most important lines of plant defense against pests. The range of cellular targets for these substances is very wide and covers metabolic pathways, macromolecules and organelles. In consequence, the plant derivatives study represents a critical situation in which toxic effects against other organisms need to be evaluated in relation to its biological benefits. The genus *Prosopis* (Fabaceae) include 44 species and is considered among the world's most damaging invasive species. The genus had been found in 129 countries globally and many more countries are climatically suitable. *Prosopis* physiology evidences a wide range of adaptability, shows the capability to growth in several adverse conditions, accumulates heavy metals and synthetizes chemical defences. Curiously, since antiquity, some *Prosopis* species around the world were described as important source of ethnopharmacological treatments for several illnesses. Toxicity against prokaryote microorganisms, fungus, parasites, mosquitoes, vertebrate animals and humans is revised in the current work. In accordance to the reviewed literature, it is possible to conclude that more specific research could make *Prosopis* species an important source of nutraceuticals and phytopharmaceutical compounds. Moreover, by its selective toxic effects, plant derivatives can be used as important source of new and successful bioactive molecules.

Keywords: *Prosopis*; Toxicity; Nutraceuticals; Phytopharmaceutical

Introduction

Plants are constantly challenged by environmental fluctuations. In response, they have developed a wide range of morphological and biochemical adaptations committed to ameliorate the effects of abiotic stress [1]. Secondary plant metabolites, such as alkaloids, glycoalkaloids, terpenoids, organic acids or alcohols, are regarded as promising sources of plant-protecting substances. These compounds are produced by a variety of plant species in practically all their organs, and they are one of the most important lines of plant defence against pests. The range of cellular targets for these substances is very wide and covers metabolic pathways, macromolecules and organelles. By modification in cellular targets, plant metabolites can affect the functioning of entire organisms [2]. In accordance to this, the plant derivatives study represents a critical situation in which toxic effects against other organisms need to be evaluated in relation to its biological benefits. Moreover, in many cases, exerted toxicity represents a desirable biological effect. Because it properties, natural products, remain an important source of new drugs, new drug leads, and new chemical entities [3]. Scrutiny of medical indications by source of compounds has demonstrated that natural products and related drugs are used to treat 87% of all categorized human diseases, including as antibacterial, anticancer, anticoagulant, antiparasitic, and immunosuppressant agents, among others [4].

The gender *Prosopis* include many species which are worldwide distributed. Some of the species are used since antiquity by native population and several ethnopharmacologic properties have been described. However, more scientific research about the gender is necessary to promote it use as source of natural medicines, insecticidal compounds and nutrients supplies.

The present work reviews *Prosopis* species research focused on its reported toxic effects and consequent beneficial medical properties with the goal to promote deep research destined to support its nutraceutical and phytopharmaceutical use.

Distribution, abundance and characteristics of genus *Prosopis* (Fabaceae): Invasive species cause ecological, economic and social impacts and are key drivers of global change. This is the case for the genus *Prosopis* (Fabaceae) where several taxa are among the world's most damaging invasive species. *Prosopis* had been found in 129 countries globally and many more countries are climatically suitable. Several *Prosopis* species have substantial impacts on biodiversity, ecosystem services, and local and regional economies [5].

Prosopis taxon is present in most of the world's hot arid and semi-arid regions as native or introduced species [6]. The genus as was described by Burkart (1976) consists of 44 species [7]. Factors that make many *Prosopis* species successful invaders include the production of large numbers of seeds that remain viable for decades, rapid growth rates, ability to coppice after damage [8,9], root systems that allow them to efficiently utilize both surface and ground water [10,11], and allelopathic and allelochemical effects on other plant species [12]. Many *Prosopis* species can also withstand climatic extremes such as very high temperatures and low rainfall, and they are not limited by alkaline, saline or unfertile soils [6,9]. Interspecific

hybridization also enhances invasiveness in many introduced regions [13]. Since a toxicological point of view, it is important to remark the capability of some species to accumulate heavy metals as chromium, lead, arsenic, cadmium, manganese, molybdenum and zinc [14,15]. Moreover, chemical defenses, as protease inhibitors, have been described as anti-herbivore mechanism of defense into the taxa [16].

The mentioned physiological plasticity implicates the production of a variety of successful secondary metabolites. Inside the context of natural products research, metabolites can be isolated and used by its beneficial selective toxic effects. The current status of toxic effects related to genus *Prosopis* and its beneficial biomedical properties are presented below [17,18].

Toxicity of genus *Prosopis* against bacterial taxa: The potential for developing antimicrobials from plants is one of the most explored fields in phytomedicine. Plant based antimicrobials have enormous therapeutic potential as they can serve the purpose without any adverse effects that are often associated with synthetic compounds; hence isolation and purification of phytoconstituents from these plants may yield significant novel antimicrobials [19].

There are only 6 species of *Prosopis* with reported antimicrobial effect (Table 1). These studies were performed against a wide number of GRAM positive and negative bacteria species, including drug resistant and multidrug resistant strains. The most common experimental approach to study the antimicrobial activity was the calculation of minimum inhibition concentration (MIC) and minimum bactericidal concentration (MBC). The antibacterial plant material derivatives better characterized were the indolizidines juliprosopine, juliprosine and prosoflorine [20,21].

Specie	Bacteria	Plant source	Cite
P. strombulifera	*Escherichia coli* *Salmonella typhi*	Fruit.	Anesini and Perez [17]. Perez and Anesini [18].
P. spicigera	*Escherichia coli* *Streptococcus mutans* *S. bovis*	Aerial parts, positive for: alkaloids, aminoacids and proteins.	Khan et al. [19]
P. glandulosa	*Mycobacterrium intracellulare*	Indolizidines from leaves.	Rahman et al. [20]
P. juliflora	*Micrococcus luteus* *Staphylococcus aureus* *Streptococcus mutans* *Bacillus subtilis* *Escherichia coli* *Enterococcus faecalis* *Klebsiella pneumoniae* *Pseudomonas aeruginosa* *Staphylococcus epidermidis* *Streptococcus pyogenes* *Salmonella typhi* *Salmonella typhimurium*	Chloroformic extract of pods. Alkaloids, Glycosides, Flavonoids and Terpenoids from leaves. Aqueos and organic extract of seed pods.	Dos Santos et al. [21] Thakur et al. [22] Tajbakhsh et al. [23]
P. cineraria	*S. aureus* *E. faecium*	Phenolic compounds derived from aerial parts.	Neghabi-Hajiagha et al. [24]
P. laevigata	*K. pneumoniae* *E. faecalis* *E. coli* *S. aureus*	Triterpenes, steroids, coumarins, alkaloids, tannins, carbohydrates and flavonoids derived from bark and leaves.	Sánchez et al. [25]

Table 1: Antibacterial toxicity of *Prosopis sp.*

Other experimental approach different from the conventional antimicrobial study is represented by the Ames´Test [26], which has been extensively used to measure the mutagenic potential of many compounds. Assays use strains of *Salmonella typhimurium* which have point mutations in the histidine biosynthetic operon that render them unable to grow in the absence of histidine. Cultures of bacterial strains in the presence of mutagenic compounds drive mutations that make microorganisms able to grow and form detectable colonies without adding histidine to the culture agar. Consequently, increased capability to grow and form colonies is indicative of mutagenic activity. In the mentioned conditions, mature pods flour of *P. alba* and aqueous extract of *P. strombulifera* were assayed and both species were described as no genotoxic [27,28].

In accordance to revised literature, the plant derivatives presented could be an appropriate source of pharmacological compounds that makes the gender *Prosopis* a promising basis for further studies and development of new antibacterial agents.

Toxicity of genus *Prosopis* against fungus taxa: Within the fungi regarded as human pathogens, members of the genus *Candida* are the most frequently recovered from fungal infections and these *Candida* infections are collectively referred to as candidiasis. The genus is an extremely heterogeneous group of over 150 species, but it is well established that only a few of these are implicated in human infectious diseases. Most cases of candidiasis have been attributed to *Candida albicans*, but other *Candida* species designated as non *C. albicans* Candida (NCAC), have been identified as frequent human pathogens [29]. On other hand, the human fungal pathogen *Cryptococcus neoformans* undergo a number of elaborate interactions with their hosts, including survival and proliferation within phagocytes as well as dissemination to the central nervous system and other tissues; almost half of these infections and has an associated mortality of over 60% [30].

Alkaloids derived from two species of genus *Prosopis*, *P. spicigera* and *P. glandulosa*, were reported as active against C. *albicans*, *C. glabrata*, *C. krusei*, *C. tropicalis* and *C. neoformans* [19,20]. The antifungal plant derivatives more precisely described were juliprosopine and juliprosine, which minimum fungicidal concentration (MFC) against *C. neoformans* was equipotent to amphotericin B. Taken together, reported activity of *Prosopis* plant derivatives make the genus an important source of compounds with a potential to solve inconveniences related to multidrug resistant and emergent species of pathogenic fungus.

Toxicity of genus *Prosopis* against parasites: Protozoal infections are a worldwide health problem, particularly in underdevelop countries [31-34], which account for approximately 14% of the world population whom are at risk of infection. Therefore, a great concern has been expressed by the WHO, as they are considered neglected tropical diseases [35]. Various studies have been conducted on protozoal diseases, including *leishmania*sis, malaria and chagas. These diseases are considered as *major* killing factors, particularly in view of the fact that various difficulties are associated with controlling the sources of infection, the high cost of treatment/prevention and poor compliance. Additional difficulties include drug resistance, low efficacy and poor safety, which may retard treatment [36]. Therefore, there is always need for the development of new and more effective drugs [37]. In this respect, natural products offer good sources for new drug discovery. It is estimated that approximately 60% of the world population still use traditional remedy methods, mainly medicinal plants or their products, because they cannot afford the cost of pharmaceutical products [38,39].

Against protozoal parasites, 3 different species of *Prosopis* demonstrate efficacy. While lectins derived from *P. farcta* are able to agglutinate *in vitro* cultured promastigotes of *Leishmania major*; alkaloids of *P. glandulosa* are toxic against promastigotes, axenic amastigotes and amastigotes in THP1 macrophage culture with a reported activity superior to pentamidine [20,40]. Antimalarial activity was reported by the capability of *P. glandulosa* and *P. juliflora* to affect *in vitro* cultures of chloroquine sensitive and resistant strains of *Plasmodium falciparum* [20,41]. And finally, intracellular amastigotes of *Trypanosoma cruzi* and free trypomastigotes of *T. brucei* are affected by the fruit methanol extract of *P. juliflora* [41].

Altogether, *Prosopis* derivatives antiprotozoal activity could be considered as a promissory field of research and drug development to control the mentioned neglected diseases.

Toxicity of genus *Prosopis* against arthropoda: Mosquitoes are well known as vectors of several disease causing pathogens. The extensive use of synthetic insecticides in the mosquito control strategies resulted to the development of pesticide resistance and fostered environmental deterioration. Hence in recent years plants become an alternative source of mosquito control agents.

Only *P. juliflora* was studied for its toxic properties against mosquitoes. Leaf organic extracts were able to exert larvicidal and oviposition altering activities. Whereas the methanolic extract is able to be toxic in larvae of *Anopheles stephensi*, *Culex quinquefasciatus*, Aedes aegypti and *A. albopictus* [42,43]; acetone extract affects oviposition of *A. albopictus* [44].

The mentioned studies would be of great importance while formulating vector control strategy based on alternative plant based insecticides in hot arid and semi-arid regions. Moreover, vectors control is one of the methods to manage, by transmission interruption, emergent diseases as dengue and chikungunya.

Toxicity of genus *Prosopis* against whole animals: The unique report about *Prosopis* sp toxicity is related to its phytoestrogenic effects on female and male Wistar rats. The study was performed to determine how pods of mesquite (*Prosopis sp*) affect animal agriculture when are used as pasture. On intact females, mesquite pod extract, altered estrous cyclicity, decreased lordotic quotient and intensity of lordosis; in ovariectomized rats, treatment induce vaginal estrus, increased vaginal epithelium height, and induced lordosis [45]. Moreover, several aspects of behavior and reproductive physiology were reported in males. Sexual behavior was disrupted after 40 days of treatment. Plant derivatives also increased testicular germ-cell apoptosis, decreased sperm quality, testicular weight, and testosterone levels [46]. Female and male effects were similar to those observed after the phytoestrogen isoflavones daidzein and genistein treatments.

Only one study was specifically performed to evaluate induced oral toxicity of *P. strombulifera* aqueous extract on BALB/c mice. Oral sub-chronic administration, 28 days dose-repeated, did not induce lethality, neuro-behavioral, anatomo-pathological, serological or biochemical alterations at 150 mg/animal/day [28].

Although, there are not similar reports about specific toxicity studies for others *Prosopis* species, an elevated number of beneficial biomedical properties were reported on different animal species (Table 2). None of these studies mentioned toxic, adverse or undesirable effects in vertebrates.

Specie	Plant source	Specie/strain	Activity	Cite
P. cineraria	Ethanolic extract of bark	Swiss albino mice	Antihyperglycemic, antihyperlipidemic and antioxidative	Sharma et al. [47]
	Alkaloids, phenolic	Swiss albino mice	Antitumoral (Ehrlich ascites carcinoma)	Robertson et al. [48]

	compounds, saponins, flavonoids and phytosterol obtained from leaves and stem bark			
	Methanolic extract from stem bark	Rabbit	Antispasmodic activity, bronchodilator and vasoconstrictive activity. (isolated tissues)	Janbaz et al. [49]
P. glandulosa	Alkaloids, glycosides, triterpenes, flavonoids and phenolic compounds obtained from leaves.	Swiss albino mice	Antitumoral (Ehrlich ascites carcinoma)	Raju et al. [50]
	DiaviteTM (dried and ground pods of P. glandulosa)	Wistar rats and obese Zucker fa/fa rats	Hypoglicemic, stimulates insulin secretion, leads to the formation of small β-cells and improves insulin sensitivity of isolated cardiomyocytes.	George et al. [51]
	Dried and ground pods	Wistar rats	Cardioprotective and infarct sparing as well as anti-hypertensive	Huisamen et al. [52]
	Dry-milled pods	Wistar rats	Suppression of the neutrophil response to contusion injury	George et al. [53]
P. strombulifera	Ethanol extract of plans	Swiss mice	Antinociceptive	Saragusti et al. [54]
P. farcta	Beans	Struthio camelus	Increased HDL cholesterol, total protein, and globulins levels; and decreases LDL cholesterol, inorganic phosphorus, and γ-GT activity.	Omidi et al. [55]
	Roots	Rabbits	reduced total cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein, and very low density lipoprotein levels.	Saidi et al. [56]
	Beens	Rabbits	Reduced the blood glucose levels.	Dashtban et al. [57]
P. chilensis	Ethanolic extract of aerial plants.	Wistar rats	anti-inflammatory and analgesic	Abodola et al. [58]
P. juliflora	Pods	Holstein-Zebu	Not significantly influence treatments regarding nutrients intake, animal performance, and feeding behavior. (84 days).	De Oliveira Moraes et al. [59]

Table 2: Beneficial biomedical properties of *Prosopis sp* described in animals.

Summarizing, with the exception of phytoestrogenic effects on Wistar rats, there are no other toxic effects related to the administration of *Prosopis* in several animal species. Altogether, evidence supports the plant derivatives research and use on whole animal models.

Reported activity of *Prosopis* on humans and human cell lines: Most of the scientific reported activities were based on ethnopharmacological and popular use of *Prosopis* plants. Mentioned folkloric uses are biased by popular available information about plant treatment benefits making a dissimilar valuation of it use around different geographical regions. As consequence of plants worldwide popular consume, it is possible to discard severe human toxicity. The reported ethnopharmacological properties, discriminated by species, are presented in Table 3. According to our research, there is just one pharmaceutical presentation of *Prosopis* derivatives; Diavite TM is a dried and ground pods of *P. glandulosa* which is prescribed as hypoglycemic agent [51].

Specie	Popular name	Properties	Cite

P. cineraria	Khejri, ghaf, jand, jandi, kalpa plant.	Antidiabetic, miscarriage preventive, malnutrition preventive, eye infections, asthma, bronchitis, dysentery, leukoderma, leprosy, muscle tremors, piles, reumathism, cardiovascular disorders.	NAS, Firewood crops [60], ICFRE [61], Shalini [62], Toky [63], Robertson et al., Janbaz et al. [49]
P. glandulosa	Honey mesquite	Dyspepsia, eruptions, eyes infections, hernias, skin ailments, throat, umbilical ailments, antidiabetic.	Kay [64], Powell [65], George et al. [51]
P. farcta	Mesquite	Colds, diarrhea, inflammation, measles, diabetes, skin diseases, prostate disorders, wound healing, chest pain, interrupt urine.	Al-Aboudi and Afifi [66], Omidi et al. [55]
P. juliflora	Algaroba, mesquite	Culinary purposes as beverages and jellies, toothache, asthma, bronchitis, conjunctivitis and skin/blood/venereal diseases.	Felkner [67], Tapia et al. [68], Hebbar et al. [69], Agra et al. [70], Senthilkumar et al. [71], Malik and Kalidhar [72]
P. alba	Unknown	Food source, dissolve gallstones, anti-bronchitic, laxative, astringent, eye infections.	Pasiecznik et al. [73]
P. strombulifera	Retortuño, retortón, mastuerzo.	Astringent, anti-inflammatory, odontalgic, anti-diarrheic.	Roig [74], Hadad and Ribas [75]
P. chilensis	Algarrobo	Protein and fiber dietary source, astringent, antiseptic.	Singh et al. [76], Rani et al. [77]

Table 3: Ethnopharmacological properties of some *Prosopis* species.

One special mention inside this section is required to the novel report about *P. strombulifera* cytotoxicity on human tumoral cell lines. Leaf aqueous extract evidenced cytotoxicity against colorectal and breast cancer cells affecting proliferation and viability in a dose and time-response manner; moreover, treatment induces clonogenic survival diminution [28]. The above mentioned research constitutes the unique report of oncologic relevance inside genus *Prosopis*.

Conclusion

Despite the numerous reports about *Prosopis* toxic and biomedical properties; only 20% of the species were scientifically analysed. Because of the bio geographical distribution and abundance of the plant material, the potential contribution of the genus as precursor of natural derivatives could be considered as under evaluated. More research need to be destined to expand the number of scientifically studied species, as well as to describe the cellular and molecular mechanisms related to the described properties.

Considering the genus biomedical potential, it is a priority to focus the research efforts to elucidate the new chemical entities provided by *Prosopis* plants to ensure its clinical applications. Chemical-analytical characterization of these natural derived products (secondary plant metabolites) and its derived natural products mimics (synthetic compounds derived from natural products) need to be considered as a priority in future investigations. The description of plant derived specific molecules represent a promissory field to develop new drugs. According to the current review, *Prosopis* derivatives could represent an important source of antimicrobial, antiparasitic, insecticidal, even anti neoplastic compounds. Moreover, chemical characterization of biological active compounds will facilitate its clinical research as alternative or complementary agents to the current available drugs.

In relation to the biological properties related to the genus, it is possible to conclude that more specific research could make *Prosopis* species an important source of nutraceuticals and phytopharmaceuticals compounds.

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Conflict of Interest

The authors report no conflicts of interest.

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