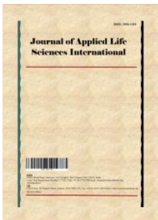

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# Creosote Bush (*Larrea tridentata*) Phytochemical Traits and its Different uses: A Review

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***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors managed literature searches, wrote the first draft of the manuscript. All authors read and approved the final manuscript.*

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## ABSTRACT

Creosote bush (*Larrea tridentata*) is a perennial shrub present in Chihuahuan, Sonoran and Mojave deserts it contains diverse metabolites; among them lignans are the most important, one of the most studied is nordihydroguaiaretic acid (NDGA), this shrub has been studied for more than seventy years due to its great variety uses. The bactericidal effect of creosote bush has been well documented, as the fungicide, nematicide, protozoa and viral effect. It has been used as an antioxidant to preserve meat in canned food. Recently research has been done on NDGA effects on anti-carcinogenic cells. There is scarce information about the use of creosote bush in livestock production. Some studies in sheep and broilers are available. The results of these research indicate that creosote bush could be used to improve productive variables in livestock and have an intestinal effect on bacteria.

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## 1. BOTANICAL DESCRIPTION

*Lazrrea tridentata* commonly known as creosote bush Fig. 1, it´s a perennial shrub that belongs to the Zygophyllaceae family; its generic name *Larrea* was given in honor to the spanish scientific J.A. Hernández Pérez de Larrea, since he was the first one to describe it [1-2]. It´s a 3-10 ft evergreen woody plant, branched from its base with small leaves, opposed, brilliant, dark to yellowish green with a lining of resin secrete by glandular trichomes during its development [3]. The flowers from 5 petal and yellow in color, grow lonely near the termination of young sprouts, they appear normally at the end of the winter or early spring, but they can bloom at any moment after a rain episode [4]. The fruit is a round capsule covered by a thick white villosity concentration [3] and contains five seeds that spread in spring and at the beginning of fall with the wind and rain [4]. Identified by the penetrating aroma and bitter flavor.

Since it´s a perennial shrub it keeps the majority of leaves at low temperature and during drought. However, extreme periodic freeze may contribute to limit the actual distribution, because when the plant freeze xylem cavitation and embolism is induced [5]. Its wide distribution in areas considered unproductive, has generated studies about its commercial value, estimating 1 million ton of dry fodder and 100,000 ton of resin [6]. However, its fodder value is questionable since it's not palatable for livestock [7].

## 2. DISTRIBUTION

Creosote bush (*Larrea tridentata*) also known as hediondilla, gobernadora, guamis or greasewood [2] is the most characteristic species of the hot desert of North America. Its abundance has been increased in response to disturbance and shepherding [8]. Creosote bush is an abundant resource in the desert zones of Mexico, it is found in Sonoran and Chihuahuan Desert, the states of North Baja California, South Baja California, San Luis Potosí, Coahuila, Durango, Zacatecas, and Nuevo León [9], about 25% of the desert areas its covered with creosote bush [10]. In the United States of America *L. tridentata* represents about 17.5 million of Ha including the following states: Arizona, California, Nevada, Texas, and New Mexico [9]. In South America specially Argentina and Bolivia, similar species to *L. tridentata* have been found [11]. It has a wide range adaptation from sea level in Death

**Fig. 1. Creosote bush (*Larrea tridentata*) specimen**

Valley California, through more than 2,500 meter above sea level in the North Mountains of Mexico [11]. Creosote bush not only thrives in areas with abundant predominant vegetation, but also is genetically adapted, its genotype varies according to the region where it is found, having two sets of chromosomes the species that grow in South America and the Chihuahuan Desert, and four sets of chromosomes those that grow in the Sonoran Desert, where the winter is mild, and rain is present during summer and winter [12]. In contrast, the plants that grow in the Mojave Desert are hexaploid (six sets of chromosomes), where they have a long and hot summer [1,12]. It´s unknown if these chromosome variations respond to the region´s weather, or if they are correlated with the amount and diversity of secondary metabolite production [13].

## 3. ETHNOBOTANY

Creosote bush has been used as folk medicine for many years by North and South America tribes [14], for the treatment of different illnesses, commonly as aqueous or ethanolic extract, in poultice using leaves and tender stems. The native healer of Southwest USA, used creosote bush leaves infusion, known as "chaparral tea" [2]. Among the main uses is for stomach pain treatment, diarrhea, and ulcers [15]. Also, for treatment of venereal diseases [14], infertility, menstruation pain, and postnatal inflammation [15-16] and as contraceptive [15]; also, in urinary tract infections [14] and cystitis [17]. The Pima Indians of Southeast of USA and Mexico used creosote bush for diabetes treatment [18]. It has anti-inflammatory and analgesic properties, and its used for neuritis and sciatica treatment [14], tooth pain [19], headache [15] breast cancer [20], allergies [21] and for liver diseases treatment [22]. The chaparral tea has been used for cold, influenza and cough treatment [15.19]. The Cahuilla tribe in the USA Southwest, used the stem and leaves infusion for cancer treatment [23]. It is considered one of the best antibiotics based in plants, because it´s effective against bacteria, virus, and internal and external parasite [24]; in addition, its fungicide activity tested with Aspergillus, Penicillium and Fusarium [25].

## 4. PHYTOCHEMISTRY

*Larrea tridentata* is a valuable source of secondary metabolite, considering that approximately 50% of their dry weight of leaves is extractable material [26]; being the resin, the main reservoir of metabolite such as saponins, sapogenins, tannins, sterols, monoterpenes, sesquiterpenes, flavonoid glycoside (19 aglycone flavonoids), a large amount of essential oils (approximately 300 volatile compounds) and 67 non-volatile compounds [2,13].

Phenolic lignans are one of the most important metabolites in *Larrea* species [13], being the most prominent in relation to dry weight, followed by saponins, flavonoids, amino acids and minerals [27]. In terms of natural chemical products, creosote bush is well known for its large amount of the acid lignan; nordihydroguaiaretic acid (NDGA) its well known as a powerful antioxidant [26,28]. It is well documented that this acid has antioxidant properties, anti-inflammatory, cytotoxic, antimicrobial and enzyme inhibitor [21,29-30]. The NDGA constitutes the 80% of all resin phenols [2] and 40 to 50% of total resin [31,32], while the resin constitutes 5 to 15% of leaves dry weight [2,31].

## 5. SECONDARY METABOLITES FUNCTION OF *LARREA TRIDENTATA*

The vegetal extracts of *Larrea* keep a wide range of pharmacological effects, this is a natural defense mechanism against threats such as microorganisms, insects, and other predatory animals [33]. Also, it has a biocide activity against bacteria [34-35], fungus, virus, protozoa, insects, and plants [36].

The resin keeps a wide range of compounds with the purpose of make the fodder less palatable, probably caused by the tannins [37], in addition it works as an antiperspirant, it forms a barrier on the surface of the leaf that decreases the transpiration more than the rate of $CO_2$ assimilation [38] and protects from UV radiation; these traits are very important for the success of species in desert environments [29]. In addition, the phenolic biopolymers and NDGA present in the resin, stem and leaves serve as a chemical defense from animal predators [29,39,40,41]

## 6. PHENOLIC LIGNANS

Lignans are natural compounds elaborated by the plant for purpose of defense and can be found in a great variety of plants and in each part of its anatomy. Its structural units are synthesized through shikimic acid pathway by the bond of two phenylpropane units linked by the central carbons of their sided chains (link $C_8$-

$C_{8'}$). The lignans were first defined as a phenylpropane dimers (C6-C3) by Haworth in 1942, who introduced the term “lignane” and subsequently change to “lignan” [42].

The lignan word is used in general, however there are different kind of lignans, among them are: lignans (contents two units $C_6$-$C_3$ linked by a bond between subunits ($C_8$-$C_{8'}$), neolignans (contents two units $C_6$-$C_3$ but with a different bond) and hybrid lignans or mixed heterodimers resulted from the coupling of monolignols or, in some cases, lignans or neolignans, with other substances like flavonoids, coumarins, xanthones, etc., that give origin to flavanolignans, cumarinolignans, estilbeno lignans, xanthone lignans, etc. [42].

In a particular way, lignans are subdivided in two groups, simple lignans and cyclo lignans; lineal type lignans were the first documented a few decades ago in desert zone plants [29]. Later, the cyclolignans and furanoid lignans were added to the list [26]. The first one represents only the link carbon-carbon through the positions 8 and 8´ of their sided chains. If oxygen is incorporated or not to the sided chain and the way, it does it can be established four subtypes of simple lignans: Dibenci bhutan; Dibencilbuthirolactone: lignan lids; Tetrahydrofurans: epoxi lignan; Furofuranes: bisepoxi lignans.

The cyclo lignans result from another additional link carbon-carbon, which results in a new ring, and 4 subtypes arise: Ariltetrahydro-naftalen, Arildihydro-naftalen, Arilnaftalen and Dibencilcyclooctadiens [42-43]. In the plant, lingan physiological functions are linked to defense activities such as fungicide, bactericide, antioxidant, and enzyme inhibitors, it can be observed its activity in some woody species where these compounds give durability, quality, color, and texture to the wood [42]. In human medicine, lignans have showed pharmacological, antioxidant, anti-herpes, fungicide, and anti-inflammatory activities for more than 70 years; and recently has been increased the studies of this compound against VIH, papilloma human virus and breast cancer [44].

## 7. NORDIHYDROGUAIARETIC ACID (NDGA)

The use of plants for medicinal purposes has been linked to human race history for a long time ago, the record shows that old cultures like Egyptians, romans, Greeks, Chinese and Babylonian used this natural resource. It´s well known that at least 2% of the botanical resources have been exploded for the extraction of bioactive molecules, and approximately 80% of the world population recur to the use of herbal medicine for primary health attention [45].

It´s known that different vegetal extracts possess diverse pharmacological effects, showing anti-inflammatory and antioxidant properties [34], biological activities against a wide range of microorganisms [36], and chemotherapy due to its phytochemical content and low toxic effect [46].

In particular, medicinal lignan awoke the interest of the scientific community a few decades ago, thanks to the discovery of compounds like podophyllin known for being highly cytotoxic extracted from the roots of species of Podophyllum [47]. The NDGA inhibits the multiple cell culture cancer proliferation that include lung cancer [48], prostate [49], gastric [50], neuroblastom [51] breast cancer [20], hepatocellular human carcinoma [52].

The lignan NDGA, has been used since the late 50´s in aging and longevity studies, because of this it has been the antioxidant no nutritious more used in experimental gerontology [53]. Until this moment, the studies involving NDGA, and other antioxidants were performed basically in rodents, fruit flies and mosquitos (laboratory animals); this situation did not allow to test the whole antioxidant effects, since they were limited by laboratory conditions [53]. Inadvertently, the application of antioxidant therapies, at that time unexplored, it occurred with livestock fed with creosote bush leaves that showed a high protein content compared to alfalfa, they were economic important for the livestock feeding in rangeland areas in the American southwest [6]. Moreover, since it’s a perennial bush, it kept a constant level of NDGA in the cattle´s diet during the whole year without variation on the different seasons [54].

Recently, the resistance to several commercial fungicide products has gained interest for the use of natural original compounds, as an alternative for the control of fungi diseases since some of them inhibit fungi growth and have demonstrated to be effective on *in vitro* and *in vivo* conditions [55-58]. Particularly the creosote bush has been studied for its antifungal action, on several occasions under *in vitro* conditions at least 17 phytopathogenic fungi of economic importance have been tested, on *in vivo* studies as ground vegetative material or as an extract incorporated to the soil to control 6 fungi in agriculture crops [59-61].

Takemoto et al. [62] mention that the antifungal activity of lignans its attributed, in part, to the inhibition of extracellular fungal enzymes: cellulase, polygalacturonase, aril-β-glucosidase and lactase. In addition, Vargas et al. [63] have observed that the β-1,3-glucanase enzyme plays an important physiological function in the fungi morphogenetic process, in β-glucane mobilization, spore cellular division and germination [64] and is involved in the interaction plant-fungi-pathogen during its attack. Vargas et al. [63] observed that *L. tridentata* extracted with dichloromethane (3 mg/ml) is capable to inhibit in 96.5% the β-(1,3)-glucanase enzyme activity; in contrast to methanol raw extract of *L. tridentata* leaves that did not show any inhibitor activity of the enzyme. When the inhibitory activity of pure lignans was performed, it was observed that NDGA (10μM) capable to inhibit 100% of the β-(1,3)-glucanase activity, while the lignan methyl-NDGA showed only 40% of inhibition. Regarding these results, it is believed that the inhibitory activity of NDGA can be related with the hydroxyil groups present in its structure, that can join to the catalytic site of β-(1,3)-glucanase and inhibit the enzyme activity as a result of that interaction. The enzymatic activation requires two functional carboxylic acids in the catalysis. The first corresponds to the general acid in the 175 glutamate, and the second to 170 glutamate, the catalytic residual involved in the nucleophilic attack over the substrate [65]. These residuals are completely kept in all β-glucanases available sequences [66], which means that the active site and the catalytic mechanism are similar inside of one family. Thus, 170 glutamate, in one polarity side from the chains of glucanase catalytic site, could be the main force of bond between the enzyme and the phenolic compounds through an hydrogen link [63]. Moreover, the antifungal pure lignan effect of NDGA and methyl-NDGA has been tested against *A. flavus* and *A. parasiticus*, and obtainment form 82 to 100% of inhibition of the growth colony diameter, with a concentration of 300 to 500 μg/ml, observing a higher fungicide effect and during much time longer with the use of methyl-NDGA [67]. Vogt et al. [68], have studied the fungicide effect of NDGA against 4 fungi phyto-pathogens *F. graminearum* (MIC 62.5 μg/ml), *F. solani* (MIC 250 μg/ml), *F. verticillioides* (MIC 125 μg/ml) and *Macrophomina phaseolina* (MIC 125 μg/ml), and obtained a strong inhibitor effect in all cases. Tequida et al. [25], showed the inhibitor effect of the alcoholic extracts of *L. tridentata* against *A. flavus*, *A. niger*, *Penicillium chrysogenum*, *P. expansum*, *Fusarium poae* and *F. moniliforme* with an inhibition percentage within the range of 41.5 % to 100%. Also, the potential fungicide effect has been studied with the resin extract of creosote bush against *Rhyzoctonia solani* and *Fusarium oxysporum* [21].

It is well known that the NDGA acts in a mechanical way as a lipooxygenase inhibitor interfering with the enzyme action [69]. It has been demonstrated that NDGA has an important effect in the cyclooxygenase pathway in the esophagus adenocarcinoma [70], while the methyl-NDGA is a potent agent inhibitor of the HIV virus replication by affecting the HIV transcription and simple herpes [71-72].

The potential use of some lignans as an insecticide has been reported early to obtain results compared with commercial synthetic pyrethroid activity, for an instance the sesquilignan Haedoxan A, isolated from the root of *Phryma leptostachya,* it is maybe the lignan well better known with insecticide properties, in combination with piperonyl butoxide, in synergy with pesticidal inhibitors of cytochrome $P^{450}$, it has an excellent insecticide activity for lepidoptera larvae and *Musca domestica*, $DL_{50}$=0.25 ng/fly. The physiological effects of these lignans are muscular relaxation, food cessation, general paralysis and death, causing similar effects like nereistoxin [73]. Moreover, there are some lignans than have been used as an effective enhancing toxicity of a wide range of insecticides, attributable to the presence of the metilendioxi group, which is responsible of the enzymatic system that carry out the oxidation and inactivation of the majority of the toxins (cytochrome $P^{450}$ oxidase) [42].

## 8. TOXICITY

Up to now, the majority of lignans seem not to be linked to intoxication problems in humans and animals, except lignans derivative of *Podophyllum* genus and NDGA. Although NDGA was used as an antioxidant for fat and butter in food in the USA for many years, it was retired by the FDA in 1968 for causing cystic nephropathy in rats. High doses of the plant extract showed hepatotoxicity, dermatitis and bile toxicity, this toxicity is eliminated when NDGA is Omethylated [74]. However, several results in studies in humans and rats support the non-toxic nature of these kinds of compounds at 300 mg/kg [72,75].

## 9. SYNERGY BETWEEN CHEMICAL ELEMENTS OF THE PLANT

Besides the NDGA, the other half of the resin has more than 20 flavonoids and methyl aglycones. The possible effects of all different flavonoids and other constituents are numerous and varied. The combined effects of these constituents point out to a synergism that amplifies the composed primary effect (NDGA), this suggests the advantage of using an extract of the whole structure leaf/branches in comparison to using a NDGA purified and synthesized preparation [27].

## 10. USE OF *LARREA TRIDENTATA* IN FARM ANIMAL PRODUCTION

As mentioned before in detail, creosote bush (*Larrea tridentata*) shows many and diverse uses according to the well documented research. Information about the use of creosote bush in farm animal production is scarce, in fact it could be said that its null. The first study with creosote bush was done by Duisberg [6] he found that both the bitter taste and the disagreeable odor of creosote bush leaves could be removed by extraction with ethyl alcohol. The residual meal after drying was edible for sheep, cattle, and goats without any additions. The carcass of a wether, fed extracted creosote bush meal for 30 days, was found to be fat in good condition, and did not possess any unusual odors or flavors. Milk from a cow and a goat fed the meal for ten days was of good quality and of normal flavor [6]. In another study [76] the effect of aqueous extract of *L. tridentata* was evaluated on the quality of poultry litter as an ingredient for beef cattle. Results showed a decrease on coliforms, molds and yeast count in the poultry litter treated with creosote bush extract also there was that a higher *in vitro* digestibility of neutral detergent fiber, so the use of the extract could be used to reduce the load of poultry litter microorganisms used to feed beef cattle without affecting feed digestibility. In another experiment [77] the aim of the study was to evaluate the effects of dietary addition of whole plant, leaves and a powder aqueous extract of *Larrea tridentata* on growth, organ weights and serum hepatic enzymes of broilers. Broilers fed the whole plant, leaves or powder aqueous extract had higher body weight and daily weight gain than control. Powder aqueous extract of *L. tridentata* reduced crop, gizzard and liver weights as compared to control, whole plant, and leaves. Broilers fed powder aqueous extract had the lowest serum hepatic enzyme concentration as compared to the control and those fed the whole plant and leaves.

In another experiment [78] the aim of the study was to evaluate the effect of *Larrea tridentata* whole plants on some traits of fatten lambs. 21 weaned Rambouillet lambs were used. Control treatment had higher final weight than treatments with *L. tridentate* inclusion. However, there were no differences for daily weight gain for all treatments. Ruminal pH values were similar for all treatments. On carcass traits, cold carcass weight, warms carcass weight and carcass longitude were higher for the control treatment. The loin perimeter was higher for the 10% inclusion *L tridentata* treatment. Moreover, other researchers [79] determined the effect of integrated diets with creosote bush biomass added as fodder for sheep intake, weight gain, pH, rumen protozoa and concentration of *Eimeria spp*, oocysts in feces. The sheep fed 5 to 10 % creosote bush had lower feed intake than the control. Weight gain, feed efficiency and rumen pH had values with non-significant differences for all treatments. The number of rumen protozoa and oocysts in feces decreased as the percentage of creosote bush in the diet increased. Other researchers [35] performed a study where extracts of creosote bush leaves were evaluated for control of *Salmonella typhimurium* in poultry pens. Solvent and the technique that obtained the highest proportion of extractable material, in vitro, were determined; its bactericidal capacity was determined and the capacity to disinfect poultry pens was evaluated, comparing disinfection with creosote bush, routine disinfection, and sanitary vacuum. At the end of the disinfection, samples were collected in floor, wall, ceiling, and curtain. Seeded in a selective medium, differential biochemical test were performed and colony forming units (CFU) were calculated. On the wall, the CFU with creosote bush decreased, while in ceiling and curtains they were similar with the routine disinfection and on the floor, lower with routine disinfection. In another study [80] the objective was to evaluate the effect of different concentrations of *Larrea tridentata* on broilers performance and three hepatic enzymes (ALT, AST, ALP) and three proteins (albumin, globulin, and total protein). The results did not show a significant difference in terms of productive variables, and hepatic enzymes in the different doses compared with the control. A decreasing linear trend was shown in albumin and total protein values as the dose of the extract increased.

## 11. CONCLUSION

It can be observed that the use of creosote bush (*Larrea tridentata*) has been varied, and this perennial bush has been studied for more than seven decades. Of all uses given to this plant, the less studied is as a part of the animal farm production, the creosote bush metabolites such as NDGA have a strong potential in animal husbandry. Nevertheless, the few studies performed with sheep and broilers, they open an opportunity to use this plant in this area. More studies are warranted in these and other animal species to corroborate the promising results found till this moment. There are some new research undergoing on swine and hen's production, specially focused on gut integrity in order to decrease the use of antibiotics as growth promoters.


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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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