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Review

Larrea tridentata (Creosote bush), an abundant plant of Mexican and US-American deserts and its metabolite nordihydroguaiaretic acid

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Abstract

Although controversial, Creosote bush, *Larrea tridentata* (Sesse and Moc. ex DC) Coville, is used to treat a variety of illnesses including infertility, rheumatism, arthritis, diabetes, gallbladder and kidney stones, pain and inflammation. Recently, it has been used as a nutritional supplement. The primary product extracted from this common plant of the arid regions of northern México and Southwestern United States is the potent antioxidant nordihydroguaiaretic acid (NDGA). It was widely used during the 1950s as a food preservative and to preserve naturals fibers. Later it was banned after reports of toxicity during the early 1960s. Renal and hepatotoxicity are also reported for chronic use of creosote bush and NDGA. This article reviews traditional and contemporary uses and pharmacology, including toxicology of this plant widely used in Mexican traditional medicine.

Keywords: *Larrea tridentata*; Gobernadora; Creosote bush; Nordihydroguaiaretic acid; Herbal medicine; Traditional medicine; Hepatotoxicity; Renal toxicity

Contents

1. Introduction 232
2. Botanical description and distribution 232
3. Phytochemistry 232
4. Ethnobotany and in vitro pharmacology related to traditional uses 233
   4.1. Reported medicinal uses 233
   4.2. Other reported uses 234
5. In vivo pharmacology and pharmacodynamics 235
   5.1. Reports on *Larrea* with positive outcomes 235
   5.2. Side effects and toxicity 235
   5.3. Experimental studies on possible additional uses of NDGA 236
   5.4. Studies on NDGA toxicity 236
   5.5. Hepatic metabolism of creosote bush and NDGA 237
6. Conclusions 237
Acknowledgements 237
References 237

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1. Introduction

Creosote bush, *Larrea tridentata* (Sesse and Moc. ex DC, Zygophyllaceae) Coville is a common shrub of North American warm deserts. Its dominance has increased within 19 million ha of lands previously considered desert grasslands in response to disturbances such as grazing (Van Auken, 2000; Whitford et al., 2001). While often viewed as an indicator of desertified conditions and the focus of extensive control efforts (Herbel and Gould, 1995) it is also an important plant with a long history of medicinal use (Timmermann, 1977). Among the proposed medicinal properties of creosote bush, the most prominent is its antioxidant effects (Sheikh et al., 1997). The family Zygophyllaceae includes more than thirty genera and approximately 250 species (Jones, 1987). *L. tridentata* is used in a variety of forms. Traditionally leaves and twigs are used to prepare a tea, but is also used in capsules and tablets, prepared for oral consumption. In México the tea is used traditionally as a treatment of kidney and gallbladder stones (Diaz, 1976). Current use is limited by reports of toxic hepatitis (Brent, 1999), and a case of cystic renal disease (Smith, 1994) associated with its chronic use. Hepatic impairment resulting from the use of conventional drugs is widely acknowledged, but there is less awareness of the potential hepatotoxicity of herbal preparations and other botanicals, many of which are believed to be harmless and are commonly used for self-medication without supervision (Stickel et al., 2000). Creosote bush is also known as chaparral and greasewood in the United States and gobernadora (governess) and hediondilla (little smelly one) in México. This review initially presents a short botanical description of the plant and an overall view of its phytochemical diversity. Then the traditional and contemporary uses reported are briefly summarised, together with in vitro studies dealing with some medicinal uses. It should be mention that most of the medicinal uses of *Larrea tridentata* are not supported by experimental or clinical studies. In the section on pharmacology, in vivo studies on the beneficial, which propose possible therapeutic additional uses, and toxic properties of both the plant and its main metabolite, nordihydroguaiaretic acid are reviewed, as well as their hepatic metabolism.

2. Botanical description and distribution

Larrea tridentata is an evergreen shrub 1–3 m high, branched and knotty. Leaves are opposite with two asymmetrical leaflets measuring ca. 1 cm in length. Leaves are glossy with a thick resinous coating secreted by a glandular epidermis of the stipules, located on the knots; the steam is woody, knotty and inerm. Flowers are complete and borne solitary in the axils, with five yellow clawed petals. The fruit is a roundish capsule, covered with a dense concentration of white hairs (De la Cerda, 1967; Nellesen, 1997). The plant discharges a penetrant odor and has a bitter flavor. It is perennial, retaining most of its leaves across the drought and low temperatures within its range of distribution, without undergoing irreparable damage. However, periodic extreme freezes may contribute to limiting the present distribution of *L. tridentata* since freezing induces xylem embolism and cavitation (Martínez-Vilalta and Pockman, 2002). Creosote bush is unpalatable to livestock and most wildlife, is usually toxic, sometimes causing death (Gay and Dwyer, 1998). Sheep, especially pregnant ewes, have been reported to die after eating the leaves (Utah State University, 2005). Creosote bush is abundant in the desert areas of the Mexican states of San Luis Potosí, Coahuila, Chihuahua, Durango, Sonora, Zacatecas, Baja California Norte and Sur, and in the Southwest of the United States in Arizona, California, Nevada, Texas and New Mexico (Rzedowsky and Huerta, 1994). Similar species are found in arid zones of South America, mostly in Argentina and Bolivia. It has been established that the plant is of South American origin, with a disjunct distribution (Lia et al., 2001).

3. Phytochemistry

Larrea tridentata is a notable source of natural products with approximately 50% of the leaves dry weight as extractable matter. The resin that covers the leaves yielded 19 flavonoid aglycones, as well as several lignans, notably including the antioxidant NDGA (Fig. 1; Konno et al., 1990). Some glycosylated flavonoids, sapogenins, essential oils, halogenic alkaloids (Argueta, 1994) and waxes were isolated from creosote bush (Romo de Vivar, 1985). *Larrea tridentata* contains about 0.1% of dry weight as volatile oils. Within the volatile fraction 67 compounds have been identified constituting more than 90% of the know creosote bush oils; the remaining 10% is a mixture of more than 300 constituents, mainly monoterpenoids and aromatic sesquiterpenoids (Mabry and Bohnstedt, 1981; Xue et al., 1988). Products from the mevalonic, shikimic and fatty acid pathways are predominant. Besides a great number of substances, the vinyl and methyl ketones contribute significantly to the creosote bush characteristic odor. Three common sterols have also been identified: campesterol, stigmasterol and sitosterol, as well as saponins of the C_{30}-ursolic type that represent less than 1% of this species dry weight (Mabry and Bohnstedt, 1981). Alkaloids have been isolated from the bark and roots, but not from the leaves and flowers (Lara and Márquez, 1996). In terms of natural products chemistry creosote bush is best known by the large amount of the lignan NDGA, which is deposited on the

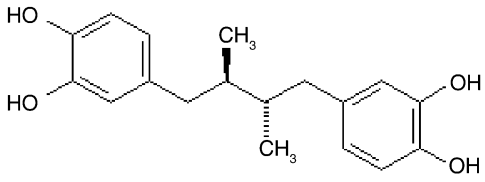

Fig. 1. Nordihydroguaiaretic acid structure.

surface of the leaves (Mabry and Bohnstedt, 1981). It has been found that between 5 and 10% of the leaves dry weight consist of NDGA, 80% of all phenolics in the resin. A study on the distribution of secondary phenolic compounds reported that flowers, leaves, green stems and small woody stems all contained NDGA, with highest concentrations in leaves (38.3 mg/g) and green stems (32.5 mg/g; Hyder et al., 2002). Due to numerous pharmacological activities of NDGA, a versatile method for its synthesis and that of a variety of derivatives was developed (Gezginci and Timmermann, 2001). Recently three new lignans, and six flavonoids and four lignans known compounds of creosote bush were isolated from the plant (Abou-Gazar et al., 2004). The epoxylignans with a tetrahydrofuran moiety showed strong antioxidant activity. NDGA and other phenols of the leaf surface deter herbivory. On the other hand, the flavonoids function as antimicrobial agents, and as protection against herbivores, UV radiation and water loss, and so are potentially important in the species success in desertic ambients (Mabry and Bohnstedt, 1981).

4. Ethnobotany and in vitro pharmacology related to traditional uses

4.1. Reported medicinal uses

Creosote bush has been used in traditional medicine to treat more than 50 illnesses (Table 1). Most common uses are associated to diseases of renal and gynaecologic origins. The plant is used as aqueous or alcoholic liquid extract of leaves and twigs; in addition, it is available in capsules and tablets for oral use, while leaves and branches can be used for poultice and fomentation. Historically, aqueous extracts of the creosote bush have been used by native healers of the Southwest region of North America, and is commonly referred to as chaparral tea. In México it is reported that an infusion of the leaves dissolves gallbladder and kidney stones when the tea is consumed throughout the day (“Agua de uso”; Martínez, 1969; Diaz, 1976; Lara and Márquez, 1996). It is used in the treatment of diseases of the liver, and as a liver tonic (Sheikh et al., 1997; Brent, 1999). Creosote bush has also been employed for kidney pain and cystitis (Martínez, 1969) dysuria (Martínez, 1969; Lara and Márquez, 1996), as a diuretic (Mabry et al., 1979b; Tyler and Foster, 1999), to treat infections of the urinary tract and venereal diseases (Timmermann, 1977; Mabry et al., 1979b; Brent, 1999). Oral decoctions and extracts of leaves and twigs have been used by the Pima Indians in the Southwest of United States and in Mexico for the treatment of diabetes (Winkelman, 1989).

Likewise, creosote bush is employed against sterility through vaginal baths with infusions of the leaves and tea (Estudillo and Hinojosa, 1988; Argueta, 1994), it is also reported to be effective against menstrual pains and postparturient inflammation (Estudillo and Hinojosa, 1988; Argueta, 1994; Brent, 1999). Whereas an infusion of the root is also used as a contraceptive (Moser, 1970; Argueta, 1994).

Externally *Larrea tridentata* has medicinal uses as tincture and salves, as antiseptic and poultice to excoriations, wounds (Timmermann, 1977; Mabry et al., 1979b; Argueta, 1994; Kay, 1996; Lara and Márquez, 1996), acne, psoriasis and dandruff (Estudillo and Hinojosa, 1988; Brent, 1999). It has also been used as salves against burns (Sheikh et al., 1997; Brent, 1999), bruises and hemorrhoids, for cicatrization (Argueta, 1994), chicken pox (Timmermann, 1977; Sheikh et al., 1997), snakebite pain, chronic cutaneous disorders (Nellesen, 1997; Sheikh et al., 1997; Brent, 1999) and allergic problems (Brinker, 1993).

Several antibiotic (Mabry et al., 1979a; Argueta, 1994), antifungal (Mabry et al., 1979a; Barragán et al., 1994; Brent, 1999) and antiviral properties (Brent, 1999) have been attributed to creosote bush. Dried chaparral is described as one of the best herbal antibiotics, being useful against bacteria, viruses and parasites, both internally and externally (Smith, 1994). The alcoholic extract of creosote bush has antifungal activity against tested species of *Aspergillus*, *Penicillium* and *Fusarium* (Tequida et al., 2002). Similarly, the ethanolic extract showed good antimicrobial activity against growth of yeast and some molds and bacteria (Verastegui et al., 1996). Among the multiples medicinal properties of chaparral, it has been mentioned as antiamoeban at low doses (Brent, 1999). Ethanolic and chloroformic extracts of creosote bush and NDGA showed a marked growth inhibition of *Entamoeba hystolitica* and *Entamoeba invadens* in culture (Segura, 1978; Mabry et al., 1979a; Calzado-Flores et al., 1995).

It is said to possess analgesic and anti-inflammatory properties, when applied as a poultice of powdered leaves (Timmermann, 1977; Argueta, 1994; Kay, 1996; Tyler and Foster, 1999), is helpful in the treatment of neuritis and sciatica (Timmermann, 1977; Mabry et al., 1979b) and has been employed as a tea to help with cramps (Brinker, 1993), toothache (Brent, 1999) and headache (Argueta, 1994). Chaparral and nordihydroguaiaretic acid (NDGA) have potent anti-inflammatory activity, possibly due to their ability to inhibit the enzyme lipoxygenase in vitro (Bokoch and Reed, 1981; Salari et al., 1984; Safayhi et al., 1992).

Other potential medicinal uses are against arthritis and rheumatism. The branches are macerated in alcohol and rubbed onto the affected area (Mabry et al., 1979b; Brinker, 1993; Argueta, 1994; Lara and Márquez, 1996; Tyler and Foster, 1999). A tea of the branches is consumed for bowel cramps and inflammation (Mabry et al., 1979b; Tyler and Foster, 1999), stomach pain, diarrhea (Argueta, 1994; Sheikh et al., 1997), ulcer and indigestion (Argueta, 1994), as an emetic (Mabry et al., 1979b; Tyler and Foster, 1999), weight-loss (Sheikh et al., 1997).

Chaparral tea has also been used in the treatment of respiratory diseases (Mabry et al., 1979b; Brent, 1999), such as cold, cough and influenza (Argueta, 1994; Brent, 1999; Tyler and Foster, 1999), bronchitis (Timmermann, 1977; Sheikh et al., 1997) and tuberculosis (Timmermann, 1977; Tyler and Foster, 1999). A large great variety of illnesses have been treated with creosote bush, such as anemia (Argueta,

Table 1
Main ethnobotanical uses of the leaves and twigs of Creosote bush

Uses	Reference
Acne, psoriasis and dandruff	Estudillo and Hinojosa (1988) and Brent (1999)
Allergic problems	Brinker (1993)
Altered blood pressure	Argueta (1994) and Sheikh et al. (1997)
Analgesic and anti-inflammatory	Timmermann (1977), Argueta (1994), Kay (1996) and Tyler and Foster (1999)
Anemia	Argueta (1994)
Antiamoebic	Brent (1999) and Segura (1978)
Antibiotic	Mabry et al. (1979a) and Argueta (1994)
Antifungic	Mabry et al. (1979a), Barragán et al. (1994) and Brent (1999)
Antineoplasic	Sheikh et al. (1997) and Tyler and Foster (1999)
Antiseptic	Timmermann (1977), Mabry et al. (1979b), Argueta (1994), Kay (1996) and Lara and Márquez (1996)
Antiviral	Brent (1999)
Arthritis and rheumatism	Mabry et al. (1979b), Brinker (1993), Argueta (1994), Lara and Márquez (1996) and Tyler and Foster (1999)
Blood purifier	Sheikh et al. (1997)
Bowel cramps and inflammation	Mabry et al. (1979b) and Tyler and Foster (1999)
Bronchitis	Timmermann (1977) and Sheikh et al. (1997)
Burns	Sheikh et al. (1997) and Brent (1999)
Chicken pox	Timmermann (1977) and Sheikh et al. (1997)
Cicatrization, bruises and hemorrhoids	Argueta (1994)
Cold, cough and influenza	Argueta (1994), Brent (1999) and Tyler and Foster (1999)
Contraceptive agent (roots of the plant)	Moser (1970) and Argueta (1994)
Cramping	Brinker (1993)
Diabetes	Winkelman (1989) and Argueta (1994)
Diseases of the liver, and as a liver tonic	Sheikh et al. (1997) and Brent (1999)
Dysuria	Martínez (1969) and Lara and Márquez (1996)
Diuretic	Mabry et al. (1979b) and Tyler and Foster (1999)
Emetic	Mabry et al. (1979b) and Tyler and Foster (1999)
Headache	Argueta (1994)
Kidney and gallbladder stones	Diaz (1976)
Kidney pain and cystitis	Martínez (1969)
Menstrual pains and inflammation after delivery	Estudillo and Hinojosa (1988), Argueta (1994) and Brent (1999)
Neuritis and sciatica	Timmermann (1977) and Mabry et al. (1979b)
Parasites	Mabry et al. (1979a) and Brinker (1993)
Snakebite pain, chronic cutaneous disorders	Nellesen (1997), Sheikh et al. (1997) and Brent (1999)
Sterility	Estudillo and Hinojosa (1988) and Argueta (1994)
Stomach pain and diarrhea	Argueta (1994) and Sheikh et al. (1997)
Toothache	Brent (1999)
Tuberculosis	Timmermann (1977) and Tyler and Foster (1999)
Ulcer and indigestion	Argueta (1994)
Urinary tract infections and venereal diseases	Timmermann (1977), Mabry et al. (1979b) and Brent (1999)
Weight-loss	Sheikh et al. (1997)

1994), altered blood pressure (Argueta, 1994; Sheikh et al., 1997) and diabetes (Argueta, 1994), as well as blood purifier (Sheikh et al., 1997) and antineoplasic (Sheikh et al., 1997; Tyler and Foster, 1999).

The beneficial effect in most of these treatments has not been demonstrated using appropriate in vivo models or clinical studies. However, two possible properties of creosote bush (and/or NDGA) for which some in vitro evidence exists seem to be of relevance for many different diseases: antibiotic and anti-inflammatory activities. In other cases this does not seem to be so, such as in diabetes and gallstones, for which, however, some experimental evidence exist (Luo et al., 1998; Arteaga, 1997). More recently, creosote bush has been introduced as a dietary supplement, mainly due to its antioxidant activity. This could explain its use and abuse in other situations, as well as the increase in toxicity reports.

4.2. Other reported uses

The essential oil has been employed in soaps and creams, as well as a shoe polish. Due to its tannin content it has been employed in tanning. The extraction, crystallization and use of NDGA from creosote bush as a food antioxidant was approved by the Meat Inspection Division of the US War Food Administration in 1943. However, in 1970 this use was banned by the US Food and Drug Administration (Timmermann, 1981). Currently, NDGA is employed as an antioxidant in the storage of natural and synthetic rubber. The resin is used as a thermofixed polymer adhesive for wood and cardboard, due to its strong antimicrobial properties, which prevent the rotting of natural fibers. It has also been used to cover capsules, tablets and pills. The whole plant has been used for house roofing and firewood (Mabry and Bohnstedt,

1981). Likewise, a boiling of creosote bush has been employed to remove scale and to unplug boilers and pipelines, as well as to clean rifle barrels (Timmermann, 1977). Cellulose with a similar quality to that obtained from conifers could be acquired from creosote bush. The later use is desirable because of the abundance of creosote bush and the need to decrease creosote populations in order to increase the productive capacity of the ecological systems it inhabits. Effective control would require that the whole plant be removed since it is a prolific root sprouter. Based on proximate nutrient profiles it could be a good food source for livestock, as it has a profile similar to alfalfa. Flour with 18–31% protein has been obtained from leaves previously extracted with ethanol (Navarro et al., 1981). However, it is necessary to remove the resin and the odor before it is used by cattle (Timmermann, 1981). On the other hand, creosote bush exhibits an ability for rapid root uptake of copper(II) ions from solution, so it may provide a useful and novel method of removing copper from contaminated soils (Gardea et al., 2001). Therefore it has been used as an indicator of soil contamination, to identify the presence and distribution of tritium near radioactive disposal areas in the Mojave Desert (Andraski et al., 2003).

5. In vivo pharmacology and pharmacodynamics

5.1. Reports on Larrea with positive outcomes

A study examining the safety of low-dosage treatment with creosote bush has been reported for subjects using creosote bush prior to initiation of the study for traditional uses including both oral and topical applications (Heron and Yarnell, 2001). In this study none of the subjects showed any history of liver disease from the use of *Larrea* in a complex herbal formula containing less than 10% of tincture, or in an extract in ricinus oil for topical use. It may be preferable to avoid the use of *Larrea* capsules because they have been associated with potentially dangerous overdosing (Heron and Yarnell, 2001). Since extracts of the creosote bush have long been used as a folk remedy for type II diabetes studies in this area are of particular interest. Masoprocol (pure NDGA isolated from the plant) significantly reduces plasma glucose and triglyceride (TG) concentrations in rats treated with streptozotocine, by increasing glucose disposal and decreasing lipolysis (Luo et al., 1998; Reed et al., 1999); it also decreases TG secretion and liver TG content in rats with fructose-induced hypertriglyceridemia, a nondiabetic model of hypertriglyceridemia associated with insulin resistance and hyperinsulinemia (Scribner et al., 2000).

The addition of a hydroalcoholic extract of creosote bush prevents the formation of pigment gallstones in hamsters (Granados and Cárdenas, 1994), and that the ethanolic extract prevents cholesterol stones by reducing the biliary cholesterol molar percent (Arteaga, 1997). This studies support the use of creosote bush in gallbladder lithiasis.

In several states and diseases, such as aging, heart disease, cancer, Alzheimer's disease, inflammatory-immune injuries/autoimmune diseases (rheumatoid arthritis, lupus, diabetes), AIDS, adult respiratory distress syndrome, etc., reactive oxygen species have a causal contribution (Frei, 1994). Creosote bush has been traditionally used in some of these disorders, and perhaps its antioxidant activity through NDGA and several other lignans could be responsible for its therapeutic benefits.

Despite the wide use of creosote bush in traditional medicine and several experimental studies that give support to these claims, there is a lack of in vivo pharmacological or clinical trials that confirm these results.

5.2. Side effects and toxicity

Chaparral products, mainly tablets and capsules of powdered leaves and twigs, have been marketed as dietary supplements, due to their antioxidant properties. However, non-recommended uses of these products have led to hepatic damage (Stickel et al., 2000). Several cases of chaparral-associated hepatitis have been reported to the U. S. Food and Drug Administration (FDA) between 1992 and 1994 (Obermeyer et al., 1995). In one report, there was evidence of hepatotoxicity in 13 of 18 patients; the predominant pattern of liver injury was characterized as toxic or drug-induced cholestatic hepatitis, jaundice and marked increase in serum liver chemistry values; in four individuals progression to cirrhosis was observed and in two individuals there was acute fulminant liver failure requiring liver transplant (Sheikh et al., 1997). In another case, a patient developed similar symptoms after taking chaparral tablets, 160 mg/day, for 2 months, documented severe cholestasis and hepatocellular injury. The serum enzyme levels were markedly elevated and severely narrowed biliary ducts were observed, without sclerosing cholangitis, distal obstruction, tumor, or stenosis (Alderman et al., 1994). Another patient developed hepatitis 2–3 months after beginning daily consumption of creosote bush leaf (proven by biopsy). The patient recovered after ceasing creosote bush intake (Batchelor et al., 1995). Yet another study reported hepatic and renal failure attributed to prolonged consumption of creosote bush products. The author of this report noted that when taken in capsule or tablet form creosote bush can cause subacute hepatitis (Gordon et al., 1995). Six patients exhibited clinical, biochemical and histological evidence of severe hepatitis after taking herbal remedies, among them chaparral. The symptoms were jaundice, fatigue, pruritus and high liver enzymes, indicating hepatocellular damage, in all biopsies portal and lobular hepatitis was found (Whiting et al., 2002).

There is also the risk of renal disease resulting from chronic chaparral tea ingestion (Spencer and Jacobs, 1999). In a case report, a 56-year-old woman was diagnosed as having numerous microscopic and macroscopic cysts in the kidney. The patient had been consuming three to four cups daily of chaparral tea during a 3-month period (Smith, 1994).

Creosote bush has been reported as an agent producing the biliary duct vanishing syndrome, observed in cholestasis induced by drugs (Chitturi and Farrel, 2001). Herbal preparations are marketed as natural and safe alternatives to conventional medicines for the prevention and treatment of a variety of ailments, however, consumers may not be fully aware of their potential side effects.

5.3. Experimental studies on possible additional uses of NDGA

This lignan posses several beneficial properties. It has been used in the treatment of the Sjogren-Larsson syndrome, a severe neurocutaneous disorder due to fatty aldehyde dehydrogenase involved in the degradation of leukotriene B4 (Willensen, 2000). This is its only clinical use reported. It modulates the expression of endothelial nitric oxide synthetase in vitro, which has implications in the treatment of cardiopathies (Ramasamy et al., 1999) and it also reduces blood pressure in rats with hypertension induced by fructose (Gowri et al., 1999). NDGA is converted by the gut microflora to estrogenic compounds, which have estrogenic activity in vitro as well as in vivo (Fujimoto et al., 2004).

Several studies suggest that NDGA could have a role in cancer therapy. NDGA and a leaf extract of a South American subspecies of creosote bush were found to exert an antitumor effect in rats (Birkenfeld et al., 1987). NDGA, at 2 mg/day p.o. for 1 week, is a potent inhibitor of hepatic toxicity and renal tumor promotion mediated by ferric-nitrilotriacetate in mice (Ansar et al., 1999). It was shown to be a possible chemoprotective agent in patients at risk or with lung cancer (Soriano et al., 1999). Moreover, non-small and small-cell lung cancer cell lines are inhibited by NDGA with an IC_{50} of 5–7 μM (Moody et al., 1998). It also reduced the frequency of micronuclei induces by methyl methanosulfonate in vivo (Diaz et al., 1999). Similar to other lipoxygenase inhibitors, NDGA induced a more differentiated state and apoptosis in several human pancreatic cancer cell lines (Ding et al., 1999), suppress breast cancer cell growth (Earashi, 1995), and also shows an additive or synergistic effect with retinoic acid on the inhibition of mammary tumor cell transformation and proliferation (Kubow et al., 2000). NDGA significantly inhibited UVB-induced signaling pathways in the human keratinocyte cell line HaCaT, which suggests it to be a potential agent in the prevention of skin cancer (Gonzales and Bowden, 2002). These reports suggest two different modes of action for NDGA in cancer. The first one as an antioxidant, preventing the harmful effect of reactive oxygen species, the other as an agent that affects genetic expression and differentiation, probably through its effect on leukotriene synthesis.

Several lignans derivatives from *Larrea tridentata* show anti-HIV activities (Gnabre et al., 1996), and several methylated NDGA were produced in the laboratory which exhibited similar or even higher anti-HIV activities than the natural compounds (Hwu et al., 1998). Of these lignans the synthetic derivative tetramethyl-*O*-NDGA, which shows the highest anti-HIV activity, inhibited (IC_{50} = 43.5 μM) the replication of herpes simplex virus in Vero cells (Chen et al., 1998) and human papilloma virus (Craigo et al., 2000).

NDGA has been used in research as an antioxidant to test the participation of lipid peroxidation in some processes. Creosote bush scavenges the superoxide anion radical O^{2-} in a dose-dependent manner (Zang et al., 1999). NDGA inhibited the alterations of airway epithelial barrier and active ion transport properties of guinea pig tracheobronchial monolayers induced by nitrogen dioxide (Robison and Kwang-Jin, 1996), the apoptotic cell death of the trophoblast layer of chorion tissues during development (Ohyama et al., 2001), and protected cultured rat hippocampal neurons against the toxicity of amyloid β-peptide, interrupting a neurodegenerative pathway relevant to the pathophysiology of Alzheimer's disease (Goodman et al., 1994).

5.4. Studies on NDGA toxicity

Besides being a potent lipoxygenase and cyclooxygenase inhibitor (Safayhi et al., 1992), NDGA is also an inhibitor of intracellular vesicular transport at concentrations between 50 and 100 μM (Drecktrath et al., 1998; Ramoner et al., 1998): it not only interrupts the secretory vesicular route, but also the endocytic pathway in human dendritic cells. Protein recycling between endoplasmic reticulum and Golgi is reversibly blocked by NDGA at 30 μM, disrupting the Golgi apparatus. However, at 100 μM it inhibits protein synthesis and alters the Golgi irreversibly (Fujiwara et al., 1998a). Likewise, it has been found that the ethanolic extract of creosote bush and NDGA have a reversible cholestatic effect in hepatocyte couplets at concentrations between 2 and 12 μg/ml (Cárdenas et al., 2000), which could be related to its inhibition of intracellular movement of transporters. NDGA reduces cellular ATP through inhibition of electron flux in the respiratory chain (Fujiwara et al., 1998b); it also inhibits the regulation of cellular volume by swelling, through an inhibition of taurine channels at 50–150 μM (Ballatori and Wang, 1997). Increases in intracellular Ca^{2+} in a concentration-dependent manner are induced by NDGA between 10 and l00 μM. This action is modulated by phospholipase A2 (Jan and Tseng, 2000). NDGA caused a dose-dependent reduction of the ovulatory rate in the isolated perfused rat ovary, with a reduction of ovarian prostaglandin and leukotriene concentrations (Mikuni et al., 1998).

The US Federal Drugs Administration prohibited the use of NDGA as food additive since it was shown to inhibit several enzymes such as peroxidase, catalase and alcohol dehydrogenase, as well as NADH-dehydrogenase and succinate dehydrogenase (Timmermann, 1981). NDGA also inhibits phospholipase A2 (Jacobson and Schrier, 1993), cytochrome P-450 (Agarwal et al., 1991) and carboxylesterases (Satoh and Hosokawa, 1998).

Reported acute NDGA LD_{50} for rodents range between 800 and 5500 mg/kg b.w. orally (Oliveto, 1972). Rats fed diets with 3% NDGA developed cortical and medullary cysts

in the kidney (Timmermann, 1977), and one case of human cystic renal disease and cystic adenocarcinoma associated to chaparral tea consumption has been reported (Smith, 1994).

5.5. Hepatic metabolism of creosote bush and NDGA

Little is known on the metabolism of creosote bush components. However, it has been reported on the hepatic processing of NDGA. The intravenous injection of 50 mg/kg of NDGA to mice resulted in a peak plasma concentration of 14.7 mg/ml, with a half-life of 135.0 min, and a clearance of 201.9 ml/min/kg (Lambert et al., 2001). The high clearance indicates that NDGA may be cleared by non-renal mechanisms. Mono and diglucuronides of NDGA have been identified in bile from mice injected intraperitoneally with 120 mg/kg of NDGA (Lambert et al., 2002). In this latter study, an LD_{50} of 75 mg/kg was established 5 days after a single i.p. dose, and an increase in alanine amino transferase was found with 50 mg/kg.

Similarly, woodrats fed with alfalfa pellets containing increasing levels of the phenolic resin from creosote bush showed increased glucuronide and sulfide conjugates level with increasing resin intake, and it seems that woodrats from the Mojave Desert tolerate more resin because they have a greater capacity for glucuronide excretion (Mangione et al., 2001).

6. Conclusions

Creosote bush and its main metabolite NDGA have shown to be useful in traditional medicine, industry and research. Although several medicinal properties of creosote bush have support in experimental studies, with some exceptions none has been tested at the clinical level. One of the main uses reported in traditional medicine is the treatment of kidney stones. However, there has not been any experimental assay dealing with this issue.

On the other hand, the toxicity of creosote bush has been demonstrated. However, as far as we can conclude from these data the reported toxic doses in humans and experimental animals always exceeded the traditional use of the plant and are often confounded with use of other herbs and potentially with lifestyle choices. Overall, prescribed appropriately traditional uses of other herbal medications appear safe. Although linkage to some adverse effects may not be discovered since problems are likely not to be reported, it is reasonable to assume that there is a wide margin of safety for many popular remedies (Elvin-Lewis, 2001).

In several in vitro assays the effective concentrations of NDGA are a range of 10–100 μM, with negative effects being reversible within this range although higher concentrations usually cause irreversible damage.

Further studies are needed to establish the therapeutic and toxic doses of creosote bush in humans and experimental animals. Creosote bush is readily available plant that potentially has many beneficial applications. However, due to some reports of toxicity care must be taken when the plant is used in traditional preparation.

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