

## Chemical and biological properties of nordihydroguaiaretic acid

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Nordihydroguaiaretic acid (NDGA) is a natural product obtained by the alkaline extraction of dried plants of *Larrea tridentata* species. Due to the biological properties presented, such as antioxidant, anti-inflammatory, antiviral and cytotoxic capacity, this compound is being increasingly studied. In this review, it was evaluated the benefits of NDGA against different animal models. Besides that, it was found that this compound has antitumor activity similar to its synthetic derivative terameprocol in prostate tumors. The hypoglycemic effect may be evidenced by the inhibition of sugar uptake by NDGA; in obesity, studies have observed that NDGA presented a positive regulatory effect for Peroxisome proliferator-activated receptors (PPAR- $\alpha$ ) involved in the oxidation of hepatic fatty acids and reduced the expression of lipogenic genes. Regarding its antioxidant potential, its mechanism is related to the ability to *in vitro* scavenging reactive substances. Although there are several studies demonstrating the benefits of using NDGA, there are also reports of its toxicity, mainly of liver damage and nephrotoxicity.

**Keywords:** Chaparral. Clinical applications. NDGA. Toxicity.

### INTRODUCTION

Nordihydroguaiaretic acid (NDGA) is a natural product obtained by extraction of dried plants of *Larrea tridentata* species (Arteaga, Andrade-cetto, Cárdenas, 2005), popularly known as “chaparral” (Hyder *et al.*, 2002). It has been used in the USA since the 1940 as an antioxidant compound for stabilization of oils and edible fats (Billinsky, Krol, 2008).

NDGA is one of the main metabolites present in *L. tridentata*, representing 80% of the phenolic compounds found in the resin that recovers its leaves (Hernández-Damián, Andérica-Romero, Pedraza-Chaverri, 2014). In addition to NDGA, these resins have flavonoids, essential oils and other phenols, which act as antimicrobial agents and radiation protection (Konno *et al.*, 1990).

The biological activity of NDGA was assessed through *in vitro* and *in vivo* studies where NDGA was effective in treating various diseases, such as cancer,

diabetes, and obesity, among others (Leon *et al.*, 2016; Lü *et al.*, 2010; Paracatu *et al.*, 2015; Stadtman, 1993; Youngren *et al.*, 2005; Zhang *et al.*, 2016). It was approved in the USA for topical use in treatment of actinic keratosis (Billinsky, Krol, 2008). In addition, Masoprocol, that is the generic name of NDGA, demonstrated promising activity as a new antineoplastic agent for topical use (Li *et al.*, 2013; Olsen *et al.*, 1991).

Although the NDGA has several biological activities, its use for therapeutic purposes is limited due to reports of toxicity, such as nephrotoxicity (Grice *et al.*, 1968), hypersensitivity contact (Olsen *et al.*, 1991), hepatotoxicity and cytotoxicity (Lambert *et al.*, 2002; Lü *et al.*, 2010).

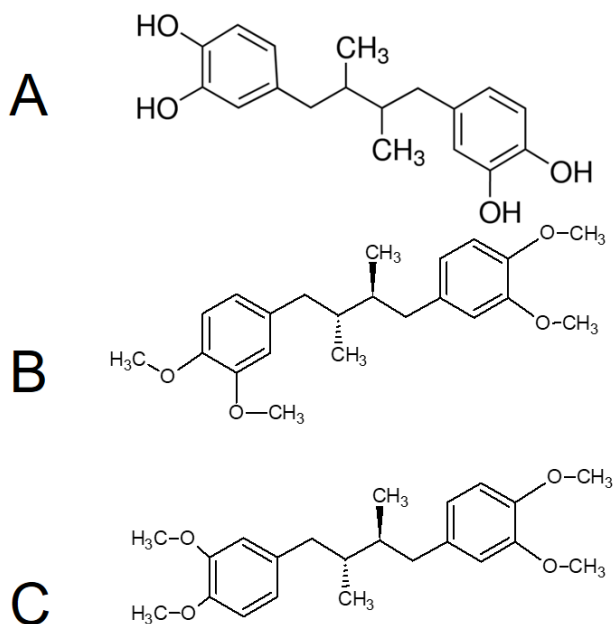
This review aims to describe the general properties of NDGA, as well as to summarize some of its biological activities, demonstrating its potential for medical use, based on *in vitro* and *in vivo* studies found in the literature, as well as discussing its possible toxicity.

### General properties of NDGA

The NDGA is the main metabolite extracted from the resin of the leaf of the creosote shrub, *L. tridentata*,

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abundant in desert areas of Mexican states (Arteaga, Andrade-cetto, Cárdenas, 2005). It belongs to the lignin family, whose chemical structure is classified as an o-dihydroxy (catechol), presenting four phenolic hydroxyl groups (Figure 1A) (Floriano-Sánchez *et al.*, 2006).



**FIGURE 1** - Chemical structure of: A) Nordihydroguaiaretic acid (NDGA); B) Terameprocol; C) Nordihydroguaiaretic tetra-O-methyl acid (M4N).

NDGA is recognized as an antioxidant compound, presenting several beneficial biological effects for health, such as, cytotoxic (Rowe *et al.*, 2008), anti-viral (Merino-

Ramos *et al.*, 2017), antioxidant (Sheikh, Philen, Love, 1997) and anti-inflammatory (Sifre *et al.*, 1993).

It is described that hydrophobicity is a very important factor for the pharmacological action and toxicological effect of chemical compounds (Cronin, 2006), because this characteristic affects the absorption, bioavailability and interactions with the hydrophobic receptor. NDGA is a hydrophobic compound, presenting a Log p = 4.48 (Paracatu *et al.*, 2015).

In relation to the pharmacokinetics of this compound at a single dose of 50 mg kg<sup>-1</sup> intravenously, the maximum plasma concentration is 14.7 mg ml<sup>-1</sup> in rats (Lambert *et al.*, 2001). In addition, approximately 99.8% of the NDGA present in plasma is protein bound, with a half-life distribution of 30 minutes, a terminal half-life of 135 minutes and renal clearance of 201.9 mL min<sup>-1</sup> kg<sup>-1</sup>. These results demonstrate that in addition to its hydrophobicity, its high degree of protein binding limits the *in vivo* bioavailability of NDGA, and the considerably high half-life may render the cytotoxic compound due to possible tissue accumulation (Lambert, Dorr, Timmermann, 2004).

### Biological activity

The biological potential of NDGA has been widely studied. When related to diseases in animal models, it is observed that the mechanisms of action of NDGA are varied (Table I).

**TABLE I** - Mechanism used by NDGA in different studies

Type of study	Mechanism of action	Authors
<i>In vivo</i>	Upregulating PPAR- $\alpha$ protein	Chan <i>et al.</i> , 2018
<i>In vitro</i>	Inhibition of lipoxigenase	Bibikova <i>et al.</i> , 2017
<i>In vivo</i>	Spermatogenesis and antioxidant	Abbas, Badran, Disi, 2018
<i>In vitro</i>	Inhibition of viral replication	Merino-Ramos <i>et al.</i> , 2017
<i>In vivo</i>	Anti-anaphylactic action	Bergren,Valentine, 2016
<i>In vitro</i>	GLUT-1 Inhibitor	Leon <i>et al.</i> , 2016

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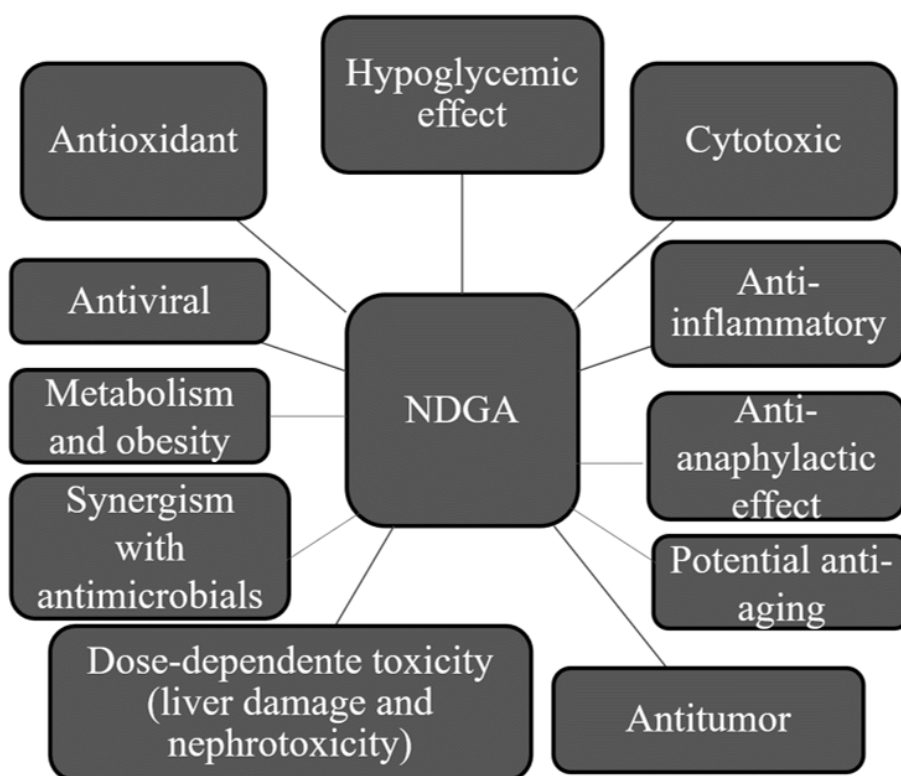
**TABLE I** - Mechanism used by NDGA in different studies

Type of study	Mechanism of action	Authors
<i>In vivo/In vitro</i>	Chemopreventive potential / Synergism	Kimura, Huang, 2016
<i>In vivo/In vitro</i>	Synergism with antibiotics	Cunningham-Oakes <i>et al.</i> , 2015
<i>In vitro</i>	Melanogenesis in human melanoma cells	Takekoshi, Nagata, Kitatani, 2014
<i>In vitro</i>	Inhibition of the G1 phase of the cell cycle	Gao <i>et al.</i> , 2011 Cui <i>et al.</i> , 2008

PPAR- $\alpha$  (Peroxisome proliferator-activated receptors); GLUT-1 (glucose transporter 1).

There are a large number of studies assessing the chemopreventive potential (Kimura, Huang, 2016; Yarla *et al.*, 2016), antioxidant (Fujimoto *et al.*, 2004) and as a selective 5-LOX inhibitor (West *et al.*, 2004). Thus,

it was observed that the versatility of NDGA allows its application in several lines of research (Figure 2) (Bergren, Valentine, 2016; Kriska *et al.*, 2012).

**FIGURE 2** - Effects and biological activities of NDGA.

## Antitumor effect

For the antitumor purposes, both NDGA and its synthetic derivative terameprocol (Figure 1B) present satisfactory results in cases of prostate tumors (Ryan *et al.*, 2008), breast cancer (Youngren *et al.*, 2005), melanoma (Lambert *et al.*, 2001) and neuroblastoma (Meyer *et al.*, 2007). In melanoma cells (malignant tumor originating from melanocytes, which are cells that produce pigment), NDGA increased the amount of intracellular melanin and the activity of tyrosinase, an enzyme responsible for production of melanin in HMVII cells (human vaginal epithelial cells) (Takekoshi, Nagata, Kitatani, 2014).

The antitumor mechanism of NDGA action is not exactly known, however, some studies have presented some mechanisms. It is known that most cells need glucose catabolism to produce energy. In this sense, the relationship between glucose uptake by cells and NDGA was evaluated. The results demonstrated that NDGA was able to inhibit and interact with the GLUT-1 (glucose transporter 1) transporter in leukemic cell lines HL-60 and U937 (Leon *et al.*, 2016).

In tumors, normally a cell cycle disorder is observed, especially at the checkpoints that occur between the G1 and S phases (Cui *et al.*, 2008). When analyzing SiHa cells from cervical cancer, NDGA has been shown to induce cell cycle arrest in G1 phase, resulting in inhibition of HPV-16 E6 expression in a dose-dependent manner (Culver *et al.*, 2005; Gao *et al.*, 2011).

Bibikova *et al.* (2017) evaluated the ability of NDGA and *Lecanicillum lecanii* extract to induce cell death. Using P388 leukemic cell cultures, it was possible to observe that both compounds induced the cells to apoptosis. An increase of cells in the SubG1 phase was observed, presenting fragmented deoxyribonucleic acid (DNA) in a dose-dependent manner. Seufferlein *et al.* (2002) observed a similar effect regarding apoptosis. The authors concluded that NDGA induces cell death due to disruption of the actin cytoskeleton and activation of protein kinases.

## Hypoglycemic effect

Considered as a metabolic disorder, diabetes mellitus is responsible for causing hyperglycemia as a

consequence of the destruction of pancreatic  $\beta$ -cells or the development of resistance to insulin action in the body (American Diabetes Association, 2010).

Dain *et al.* (2016) evaluated the potential of NDGA in decreasing glucose levels, there is the study of In this study, mice were induced to diabetes by the administration of fatty acid once a month at the concentration of 6.25 mg kg<sup>-1</sup> for 12 months and received intraperitoneally treatment of 1.9 mg kg<sup>-1</sup> NDGA once a month for the same period. They found that the treatment with NDGA resulted in a decrease in glycemic levels following oral glucose tolerance and glycated hemoglobin tests. The tests were performed on day 40 and at the end of the sixth and tenth month of treatment. The possible mechanism of NDGA action against diabetes is through the glucose transporter 1 (GLUT1) receptor, responsible for controlling the entry of glucose into cells.

Using the glucose uptake and glucose monitoring in human erythrocytes, where the GLUT1 plays the role of the main transporter, the data presented suggest that NDGA competes with D-glucose to bind to the GLUT1 receptor (Leon *et al.*, 2016).

It also stands out the inhibitory effect of NDGA on the  $\alpha$ -glucosidase,  $\alpha$ -amylase and dipeptidyl peptidase 4 enzymes, thus suggesting a possible mechanism for its use as an antidiabetic compound (Roskar, Strukelj, Lunder, 2016).

## Effect on metabolism and obesity

Obesity is a physical condition that becomes increasingly common, especially in American individuals, due to dietary habits based on soft drinks and extremely caloric foods associated with lack of physical exercise (Seidell, Halberstadt, 2016).

In a study where the mice were induced to obesity through the American Lifestyle Induced Obesity Syndrome (ALIOS) diet, which consists of a high fat modified diet, accompanied by drinking water supplemented with high fructose corn syrup. The mice were divided into 3 groups: a group that received only standard feed; another received only the ALIOS diet; and finally a group that received the ALIOS diet plus the treatment with NDGA, 2.5 g kg<sup>-1</sup>. The experiment

lasted 8 weeks. They found that rats that consumed only the ALIOS diet developed obesity, metabolic imbalances, including hepatic steatosis with liver damage, dyslipidemia, insulin resistance and glucose intolerance, and exhibited increased expression of key enzymes of genes involved in liver lipogenesis. On the other hand, animals fed with ALIOS diet supplemented with NDGA presented a positive regulatory effect for peroxisome proliferator-activated receptors (PPAR- $\alpha$ ) involved in the oxidation of hepatic fatty acids and reduced the expression of lipogenic genes, also showed increased expression of antioxidant enzymes (Chan *et al.*, 2018).

With the objective of examining the effects of NDGA dietary administration on the gene expression involved in lipid homeostasis in the liver, skeletal muscle and adipose tissue, Zhan *et al.* (2016) fed rats with a 60% fructose diet supplemented with 2.5 g kg<sup>-1</sup> NDGA for 16 weeks. The results showed that chronic dietary treatment with NDGA could attenuate hypertriglyceridemia induced by a diet rich in fructose and hepatic steatosis (accumulation of thyroglobulin). In addition, the analysis indicated that NDGA increases the expression of enzymes involved in the oxidation of liver fatty acids and proteins that facilitate the transport of fatty acids. Based on the experimental data, the authors concluded that the beneficial effects of NDGA in triglycerides and steatosis are carried by inhibiting lipogenesis, and increasing the functional expression of key genes for enzymes/ proteins involved in the pathway of  $\beta$ -oxidation of fatty acids in liver and skeletal muscle, which corroborates the previously described study.

### Synergism with antimicrobials

There is great difficulty in treating infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) (Fry, Barie, 2011). The NDGA shows antimicrobial activity, with possible action on the bacterial membrane. The NDGA among with the antibiotics gentamicin, neomycin and tolbramycin, were tested in isolates of MRSA and methicillin sensitive *S. aureus* (MSSA). The results demonstrated that NDGA could alter membrane permeability in bacteria, potentiating the response to antimicrobial agents in vitro and allowing a combination

of antibiotic accumulation at the target site (Cunningham-Oakes *et al.*, 2015).

In a study by Ohene-Agyei *et al.* (2014), the ability of natural products to increase the microbial activity of antibiotics was evaluated. NDGA had a synergistic relationship with known antibiotics, for example, erythromycin, chloramphenicol and tetracycline. The result of this union was satisfactory because the time in which the bacteria was exposed to the drug increased. As demonstrated, the NDGA is able to act on the efflux pumps present in the bacterial cells, altering their activity and consequently decreasing the drug's output from the cell.

### Antioxidant activity

Antioxidants are compounds that inhibit the formation of free radicals or prevent the stage of propagation of these reactions, through the donation of hydrogen, such that the target molecule becomes stable, acting in delaying or preventing oxidation (Broinizi *et al.*, 2007; Soares, 2002).

Naturally, the metabolism of oxygen generates a significant amount of reactive species. The hydroxyl radical, which can be formed through different reactions, is considered one of the most reactive radical species due to the potential damage caused in DNA and proteins, characterizing the so-called oxidative stress (Boyd, Mcguire, 1991; Hájková, Barek, Vysko, 2017; Stadtman, 1993).

The use of natural antioxidant compounds has gained importance due to the low toxicity to the organism (Moure *et al.*, 2001). NDGA is a natural compound that has considerable antioxidant properties, and has been used for a long time in folk medicine (Arteaga, Andrade-cetto, Cárdenas, 2005). Its potential is related to the ability to sequester reactive species *in vitro* such as peroxyxynitrite, singlet oxygen, hydroxyl radical and superoxide anion, decreasing the probability of developing diseases involved with oxidative stress processes, such as cancer (Floriano-Sánchez *et al.*, 2006).

The antioxidant capacity of a compound is a great pharmaceutical interest. Considering this question, Huang *et al.* (2017) evaluated the potential of NDGA in an animal model of induced transient ischemia.

Through intracerebroventricular injection, the animals received a concentration of 0.2 mg kg<sup>-1</sup> of 2,5-bis (3,4-dihydroxybenzylidene) cyclopentanone, which is an analog of NDGA, while another group received edavarone, a standard drug. The NDGA analogue evaluated showed satisfactory results. In addition to the reduction of the infarct region, as a consequence of the ischemic episode, the antioxidant potential can also be confirmed in the pre-treated rats, making the NDGA very promising in the treatment of stroke (Candelario-Jalil, 2009).

### Anti-anaphylactic effect

An anaphylactic shock occurs when the immune system develops a severe hypersensitivity reaction to a substance considered as an allergen to the body resulting in airway problems and the release of inflammatory mediators (Kastner, Harada, Wasserman, 2010; Sampson *et al.*, 2006; Simons *et al.*, 2011).

NDGA has several interesting properties for the research, such as its antioxidant effect, arterial hypertension antagonist and lipoxygenase inhibitor (5-LOX), which aroused the interest of the possible application of this compound in cases of anaphylactic shock (Kriska *et al.*, 2012; Shen *et al.*, 2015).

The anti-anaphylactic potential of NDGA was evaluated in an animal model using guinea-pigs sensitive to ovalbumin. The efficacy of the compound was evaluated by the quantification of leukotrienes 4 (LT4), where the groups previously treated both intravenously and through aerosols presenting lower levels of LT4. The possible mechanism used by the NDGA, according to the study, occurs through 5-lipoxygenase blockade, which consequently inhibits the synthesis of leukotrienes, which are involved in bronchoconstriction (Bergren, Valentine, 2016).

### Antiviral effect

Viruses are considered obligatory intracellular parasites due to their characteristic of using the machinery and resources of a host cell, so they can multiply and infect other cells (Chan, Gack, 2016).

In antiviral studies, NDGA was able to inhibit the multiplication of viruses such as dengue (Soto-Acosta *et al.*, 2014). Recently, NDGA and its methylated derivative nordihydroguaiaretic tetra-O-methyl acid (M4N) (Figure 1C) were evaluated in a model using West Nile flavivirus (WNV) and Zika virus, responsible for causing meningitis and encephalitis and congenital anomalies, respectively. The obtained results demonstrated that both compounds can inhibit viral replication. It is believed that the inhibition is related to the metabolic alterations of the cells that prevent the replication of the viruses, which present obligate intracellular parasite conditions (Merino-Ramos *et al.*, 2017).

### Potential anti-aging

Publications related to aging are increasing and can provide important information to deal with this implication (Kerschner, Pegues, 1998).

In order to evaluate agents that aim to increase life expectancy and postpone the onset of diseases, NDGA has been shown to prolong the life span of mice, as well as delay several age-related health problems (Strong *et al.*, 2008). The same effect can be observed in experiments with *Drosophila melanogaster* (*Drosophila*). The responses presented different aspects in flies and mice. However, NDGA has demonstrated that it can prolong the life span of mice and *Drosophila*, suggesting that its performance can be conserved phylogenetically (Spindler *et al.*, 2015).

### Toxicity

The NDGA is the active compound present in the Chaparral plant (Arteaga, Andrade-cetto, Cárdenas, 2005). Studies have indicated cases of hepatotoxicity in patients who received chaparral, and cases of liver damage after chronic ingestion of chaparral (Grant, Boyer, Erdman, 1998). Sheikh, Philen, Love (1997) concluded that the use of chaparral may be associated with acute irreversible liver damage with chronic fulminant hepatic failure.

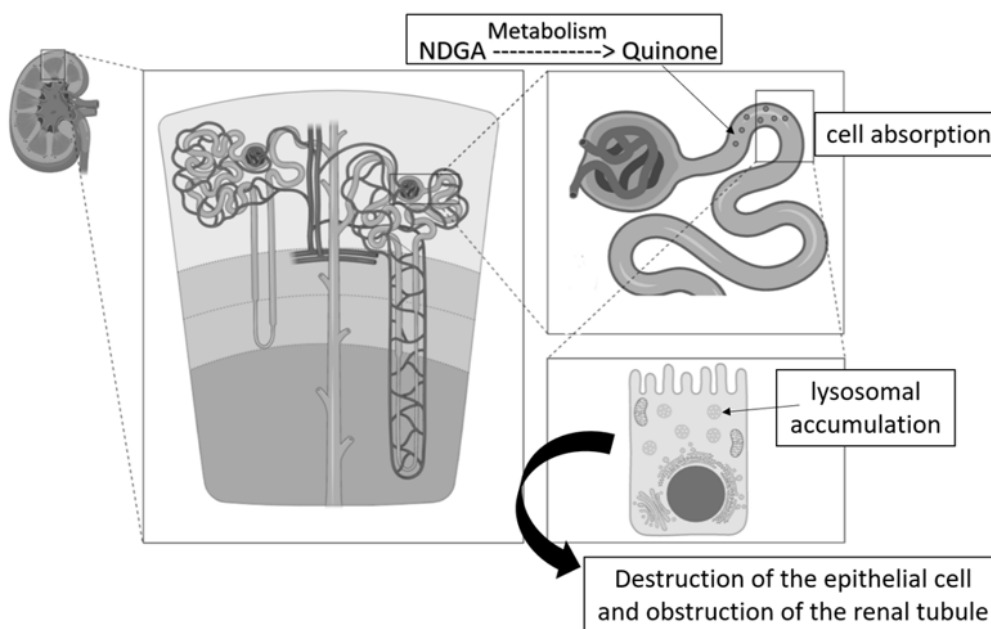
In a model of *in vitro* rat hepatocyte cultures aimed to evaluate the hepatological and pro-oxidant potential

of NDGA, it was observed that the compound exerts adverse prooxidant effects on hepatocyte cultures, but showed beneficial antioxidant activity in macrophages, thus suggesting that the NDGA has a potential to act as a pro- and antioxidant depending on its concentration (Sahu, Ruggles, O'Donnell, 2006).

Acute exposure to NDGA, depending on the dose, results in lethality in mice. The toxicity of NDGA is marked by elevation in serum levels of the enzyme alanine aminotransferase. Although mouse hepatocytes are more sensitive to NDGA-induced cytotoxicity than

human melanoma cells, these findings aim to reduce the parenteral administration of NDGA, without excluding its use in topical formulations (Lambert *et al.*, 2002).

Even the liver being the main metabolizing organ of xenobiotics (De Carvalho *et al.*, 2013), it was demonstrated that NDGA can cause cystic nephropathy in rats. Its occur due to the quinone resulting from the metabolism process of NDGA absorbed by the proximal tubular epithelium and accumulate in the lysosomes, thus leading to the destruction of tubular epithelial cells and tubule blockage (Goodman *et al.* 1970; Evan, Gardner, 1979) (Figure 3).



**FIGURE 3** - Renal cell death caused by NDGA.

Lambert *et al.* (2002) have shown that the NDGA nephrotoxicity can be brought about by methylation of the hydroxyl groups of catechol. In the literature it is also found that NDGA is used as a model of induction by renal disease drug (Evan, Gardner, 1979; Gardner, Evan, Reed, 1986; Goodman *et al.* 1970).

In view of the clinical evidence of hepatotoxicity and nephrotoxicity caused by NDGA ingestion, Spindler *et al.* (2015) investigated their toxicity and relationship to pathologies leading to mortality. Based on this, they

found an association between NDGA consumption and an increased incidence of liver, lung and thymus tumors.

In contrast, Zúñiga-Toalá *et al.* (2012) evaluated the protective effect of NDGA in renal injuries induced by ischemia and reperfusion (I/R), oxidative stress and changes in antioxidant enzymes and mitochondrial function in rats. The data obtained by them showed that NDGA protects against damage induced by I/R, and its protective effect is related to renoprotection, associated with the prevention of oxidative stress. Yam-Canul *et*

*al.* (2008) studied the effect of NDGA on nephrotoxicity induced by potassium dichromate (K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>) and oxidative stress. The results showed that NDGA was able to improve the structure and reduce the damage in renal function evaluated by histopathological and biochemical analysis. The protective effect of NDGA in this study was also associated with improved oxidative stress, suggesting that the antioxidant properties of NDGA are involved in its renoprotective effect.

In addition, NDGA and its derivative terameprocol are recognized for their ability to activate NRF2 transcription factor (erythroid-related nuclear factor 2). This activation is promising for the treatment of several chronic diseases (Robledinos-Antón *et al.*, 2019). It can be explained by the cytoprotective effects of Nrf2, which is the main regulator of genes that encode many antioxidant and detoxifying enzymes. (Aminzadeh *et al.*, 2013)

In concern of the data exposed above, it is possible that the difference between the protective and toxic effects of NDGA may be related to the daily dose administered. The protective effect of NDGA *in vivo* was observed at 5 to 100 mg/ kg/ day, while toxic effects were observed at doses greater than 1 g/ kg/ day (Gardner, Evan, Reed, 1986; Goodman *et al.*, 1970; Yam-Canul *et al.*, 2008; Zúñiga-Toalá *et al.*, 2012).

## FINAL CONSIDERATIONS

NDGA, the main metabolite present in *L. tridentata*, besides presenting antioxidant action, has been shown to have promising applications in the treatment of several diseases, such as cardiovascular diseases, neurological disorders and cancers. However, in relation to its safety and toxicity, its clinical application is limited, presenting several reports of nephrotoxicity and hepatotoxicity.

In the literature, many biological activities of NDGA have already been described (Goodman *et al.*, 1994; Guzmán-Beltrán *et al.*, 2016; Lü *et al.*, 2010) its reported benefits are diverse and can aid in the prevention or reduction of clinical manifestations. High-incidence diseases, such as diabetes (Anjaneyulu, Chopra, 2004) and neoplasms (Seufferlein *et al.*, 2002) are the main targets for this compound. When considering all these factors, it becomes clear the importance of more studies

involving NDGA, evidencing new benefits. The results may serve as basis for further research, so all the biological properties of the compound can be exploited and applied in therapy.

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