Aporphine alkaloids and their antioxidant medical application: From antineoplastic agents to motor dysfunction diseases

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Abstract: One of the biggest challenges in the modern medicine and the food industry is to provide with compounds that should have the property to be antioxidant that, proportionally, can be accompanied with pharmacological activities to be used in chronic clinical treatments. This means, compounds that can extend the shelf life of foods and drugs avoiding its decomposition by oxidation and, at the same time, to afford potent drugs against various diseases with minor side effects. Thus, aporphine alkaloids have been the group of nitrogen compounds more studied and with a wide therapeutic application. Examples such as (−)-boldine (**12**), (−)-liridinine (**15**), (+)-lirinidine (**16**) and glaucine (**24**) have been studied for its interesting antioxidant activity and, in case of **24**, synthetic modifications have managed to generate derivatives that exhibit more efficient antioxidant activity in comparison with carboxy group-containing agent alone and aporphine derivative alone. Thus, clinical treatment against oxidative stress-related diseases, as Parkinson´s disease, anticancer, antinociceptive, therapeutic applications among other mentioned in this review, they give the possibility of using these aporphine alkaloids of low cytotoxicity as an excellent alternative tool in the development of new therapeutic patterns using the duplicity; biologically active ingredient-antioxidant.

Keywords: Aporphines; oxoaporphines; antioxidant, free radical scavengers; oxidative stress; Parkinson's disease; anticancer; antinociceptive.

1. INTRODUCTION

The oxygen is the molecule that for nature allows to the living organisms be able to develop the cellular and morphologic activities that need for their surviving. Although this molecule can be combined together with atoms of the same specie to give reactive molecules as ozone (O_3), for the adequate protection of the biosphere by ultraviolet radiation, also it is carried out by different atoms to generate complex structures in the cellular metabolism. Nevertheless, some species of oxygen can be absolutely harmful and its effect dangerous when acting continuously and permanently in the living systems.

In this sense, reactive oxygen species (ROS) generated inevitably play a useful role in signal transduction, but excessive production of ROS leads to oxidative stress damage to cellular structures, such as lipids, DNA and proteins, which is a result of imbalance between the antioxidant system and the formation of ROS *in vivo* [1]. As a result, oxidative stress is clearly associated with the etiology of a wide range of chronic and acute disease such as malignant tumors, inflammation, cataracts, Parkinson's and Alzheimer's disease, hypertension, diabetes, atherosclerosis, cardiovascular diseases, cell death, and some immune disorders and the aging process [2].

By definition, an antioxidant is ''any substance that, when present at low concentrations compared to those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate'' [3]. They have the aptitude to scavenge ROS by donating hydrogen atom or electron, chelating metal catalysts, activating antioxidant enzymes and inhibiting oxidizes. In order to protect the body from such effects, in addition to antioxidant enzymatic system, there are non-enzymatic biomolecules and proteins in living organisms, which act as antioxidant and free radical scavengers. Notwithstanding, there are two major groups of antioxidants in living cells:

enzymatic antioxidants and non-enzymatic antioxidants. These groups are divided into several subgroups. The enzymatic antioxidants are divided into primary and secondary enzymatic defenses [4]. The primary defense is composed of three important enzymes that prevent the formation and neutralize free radicals: glutathione peroxidase, which donates two electrons to reduce peroxides by forming selenols and also eliminates peroxides as potential substrates for the Fenton reaction; catalase, which turns hydrogen peroxide into water and molecular oxygen, one of the most important and efficient antioxidants known today, when just one molecule of catalase converts billion molecules of hydrogen peroxide [5]; and finally, superoxide dismutase, which converts superoxide anions into hydrogen peroxide as a substrate for subsequent catalase action. The secondary enzymatic defense includes glutathione reductase and glucose-6-phosphate dehydrogenase. Glutathione reductase reduces glutathione from its oxidized to its reduced form, and by this recycling, to continue neutralizing more free radicals [6].

Nowadays, most food and pharmaceutical products contain synthetic antioxidants. These compounds are added to food in order to prolong product shelf life, mainly by preventing the oxidation of unsaturated double bonds of fatty acids. In pharmaceutical products to antioxidants are added to enhance the stability of therapeutic agents that are susceptible to chemical degradation by oxidation. The two most common synthetic antioxidants used today are butylated hydroxyanisole (BHA) and butylated hydroxyltoluene (BHT). Propyl gallate and *tert*-butylhydroquinone (TBHQ) are other widely used synthetic antioxidants in the processed-food industry. Notwithstanding, the use of new compounds that could have a wide food application and in the scope of the health, avoiding with it the use of synthetic antioxidant due to possible cytotoxicity and side effects, associated much times with pro-carcinogenic effects by formation of heterocyclic amine (HA) precursors [7]. Hence, they make viable the possibility of studying new

antioxidant patterns that can be clearly miscible with the food industry and in the generation of new drugs against the cellular oxidative stress.

Thus, in this review, we will do a revision of the most abundant group of nitrogen compounds and wide chemical diversity in nature as the aporphine alkaloids. In this sense, aporphines either from vegetable or others generated by means of synthetic routes have been recognized in diverse medical and therapeutic applications due to its wide benefit and bioavailability. Many of the scopes of antioxidant application are focused in this review in the clinical administration derived of their pharmacological properties and reflected in the hypertension. antineoplastic activity, antiplasmodial, diabetes, obesity-related cardiovascular disease together with the Parkinson's and oxidative stress-related disease.

For instance, it is feasible to extract and to purify different alkaloids from leaves of *Nelumbo nucifera Gaertn*. cv. *Rosa-plena*. These compounds include liriodenine (**1**), lysicamine (**2**), (-)-anonaine (**3**), (-)-asimilobine (**4**), (-)-caaverine (**5**), (-)-*N*-methylasimilobine (**6**), (-)-nuciferine (**7**), (-)-nornuciferine (**8**), (-)-roemerine (**9**), 7-hydroxydehydronuciferine (**10**) and cepharadione B (**11**) among other (Figure 1). The antioxidant activity of the alkaloids was examined by antiradical scavenging, metal chelating and ferric reducing power assays. The results have shown that these alkaloids have antioxidative activity and antiproliferation activity against human melanoma, prostate and gastric cancer cells. In this sense, the results obtained with 7-hydroxydehydronuciferine (**10**) showed an interesting inhibition in the proliferation of melanoma, prostate and gastric cancer cells. Maybe that hydroxyphenanthrene can be an interesting pharmacological moiety to be considered due to planarity and easy intercalation [8]. Another example of aporphine alkaloids isolated with antioxidant and other interesting pharmacological properties as antiplasmodial activities is the crude extract of the bark of

Dehaasia longipedicellata, wherein some morphinandienones and two aporphine as (-)-boldine (**12**) and (-)-norboldine (**13**) were assessed (Figure 2). The results shown a moderate antiplasmodial activity with IC_{50} values ranging from 0.031 to 30.40 μM and low anti-oxidant respect to other isolated alkaloids. However the cytotoxicity against a few cancer and normal cell lines was assessed, being **13** exhibited potent cytotoxicity towards pancreatic cancer cell line BxPC-3 with an IC_{50} value of 27.060 ± 1.037 μM, and all alkaloids showed no toxicity towards the normal pancreatic cell line (hTERT-HPNE) [9]. Notwithstanding, other reports shown an important antioxidant and antiproliferative activities of **12** than known members of the aporphine group [10]. Moreover, some authors several years ago found that **12** has a recognized and potent antioxidant activity. Thus, in a later study, the same authors report that boldine concentrations-dependently inhibited the peroxidative (accumulation of thiobarbituric acid reactive substances) and lytic damage (trypan blue exclusion and lactate dehydrogenase leakage) to isolated rat hepatocytes induced by *tert*-Bu hydroperoxide (TBOOH) [11]. Such results conclude that pre-incubation of the hepatocytes with boldine prevented lipid peroxidation and was as effective in protecting the cells against the damage caused by the subsequent addition of TBOOH.

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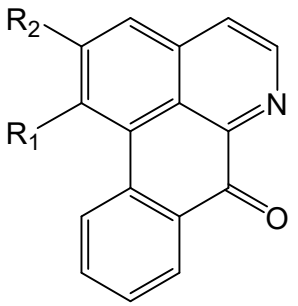
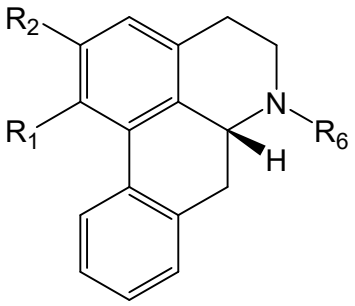
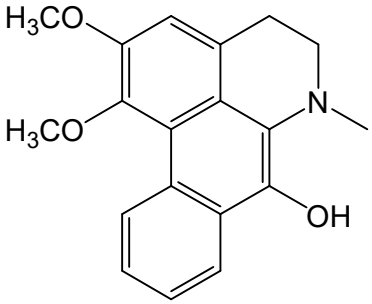


(1); $R_1 = R_2 = -OCH_2O-$
(2); $R_1 = R_2 = OCH_3$



(3); $R_1 = R_2 = -OCH_2O-$, $R_6 = H$
(4); $R_1 = OCH_3$, $R_2 = OH$, $R_6 = H$
(5); $R_1 = OH$, $R_2 = OCH_3$, $R_6 = H$
(6); $R_1 = OCH_3$, $R_2 = OH$, $R_6 = CH_3$
(7); $R_1 = R_2 = OCH_3$, $R_6 = CH_3$
(8); $R_1 = R_2 = OCH_3$, $R_6 = H$
(9); $R_1 = R_2 = -OCH_2O-$, $R_6 = CH_3$



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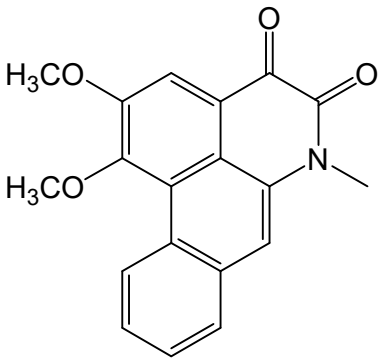
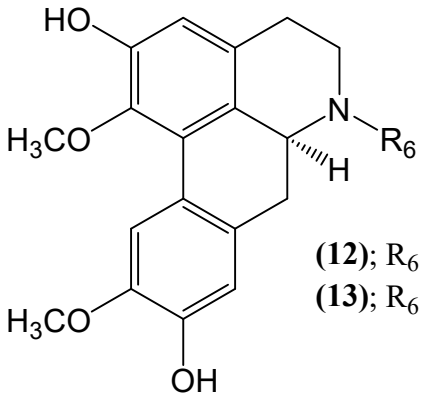


(11)

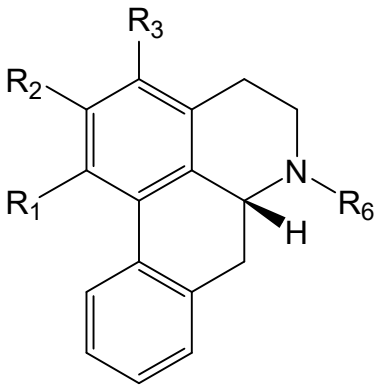
Figure 1. Chemical structures of alkaloids **1-11** isolated from leaves of *N. nucifera.*



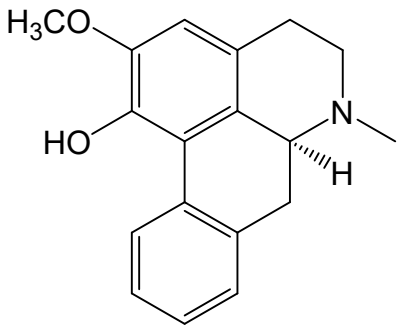
(12); $R_6 = CH_3$
(13); $R_6 = H$

Figure 2. Chemical structures of (-) boldine (**12**) and (-)-norboldine (**13**).

On the other hand, some reports from leaves of *Liriodendron tulipifera* have identified aporphines, oxoaporphine, coumarin, sesquiterpene lactone, benzenoids, cyclitol and steroids, Hence, (+)-Norstephalagine (**14**) was isolated from the first time together with other aporphines such as (**2**), (**3**), (**5**), (**8**), (−)-liridinine (**15**) and (+)-lirinidine (**16**) (Figure 3). Such compounds were screened for their antiradical scavenging, metal chelating and ferric reducing power activities. The results of this study have showed that these alkaloids have antioxidative activity. The study has also examined the chemopreventive property of the isolated alkaloids against human melanoma cells A375. The results shown that (**2**), (**3**), (-)-liridinine (**15**) and (+)-lirinidine (**16**) significantly inhibited the proliferation of melanoma cells. Therefore, these results have shown that certain alkaloids have antioxidative activity and chemopreventive activity in skin melanoma cells [12].



(14); $R_1 = R_2 = -OCH_2O-$, $R_3 = OCH_3$, $R_6 = H$
(15); $R_1 = OCH_3$, $R_2 = OH$, $R_3 = OCH_3$, $R_6 = CH_3$

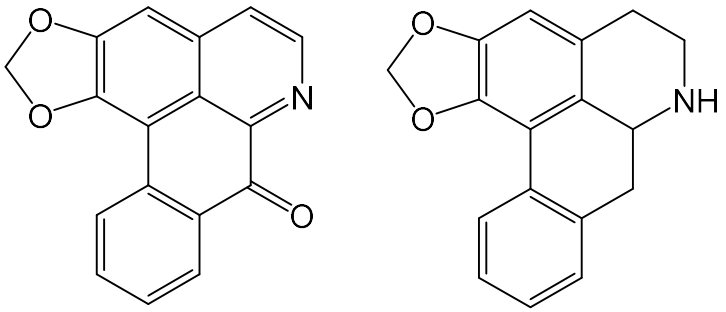


(16)

. **Figure 3.** Chemical structures of compounds **14-16** from leaves of *L. tulipifera*.

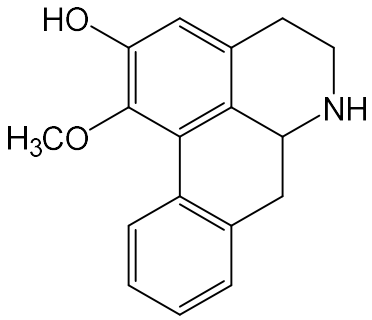
The antimicrobial activity of some compounds also is related with the antioxidant property, being the presence of hydroxyl groups a possible key in the therapeutic role. Thus, the antioxidant capacity by oxygen radical absorbance capacity (ORAC)-FL method and antimicrobial activity using the broth microdilution method of aporphinoids such as liriodenine (**17**), anonaine (**3**) and asimilobine (**18**) isolated from the bark of *Annona salzmannii* A. (Annonaceae) were evaluated (Figure 4). In the scope of antioxidant activity, the most active alkaloid was **18** with ORAC value of 2.09 relative trolox equivalent. Instead for antimicrobial activity, some alkaloids showed significant minimal inhibitory concentration (MIC) values in the

range of 25-100 μg mL^{-1} [13]. Therefore, these results can show that the antioxidant activity is related with the presence of hydroxyl group in **18**, though another biological property as antimicrobial could be based in the planarity of some aporphine moities, which can afford an intercalator agent in an anticancer treatment.



(17)

(3)



(18)

Figure 4. Alkaloids isolated from the bark of *A. salzmannii*.

Sometimes some compounds can be used in several chronic diseases and, in the case of antioxidant alkaloids, certain health conditions can help in its treatment using aporphines. Thus, boldine (**12**), a one of major aporphine alkaloid found in the Chilean boldo tree, which is a potent antioxidant, it was used in order to study the endothelial dysfunction in hypertension using spontaneously hypertensive rats (SHR), the most used animal model of hypertension. Thus, the

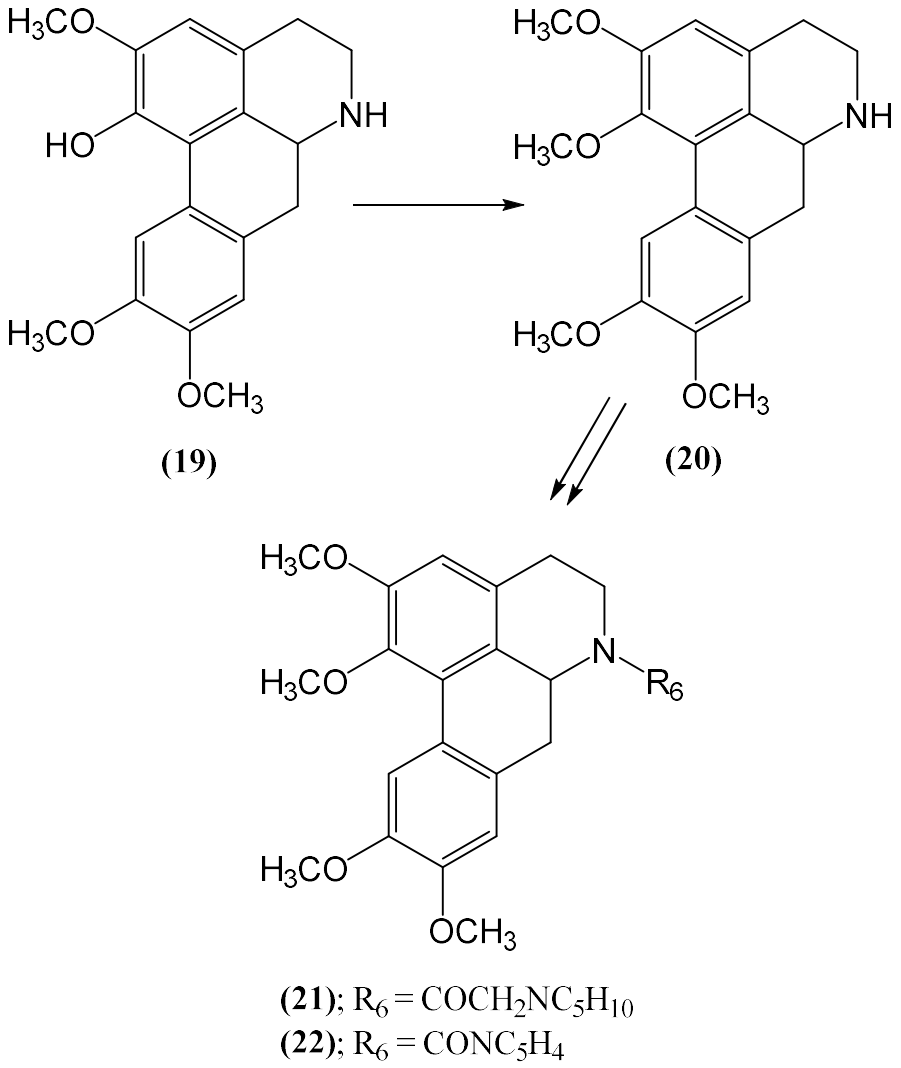
control SHR displayed higher systolic blood pressure (SBP), reduced endothelium-dependent aortic relaxation to acetylcholine (ACh) and increased aortic superoxide and peroxynitrite production. Boldine treatment significantly lowered SBP in SHR. Boldine treatment enhanced the maximal relaxation to ACh in SHR, whereas the sensitivity to ACh was increased in SHR aorta. Boldine treatment enhanced sensitivity, but was without effect on maximal aortic relaxation responses. These results show that **12** exerts endothelial protective effects in hypertension, achieved, at least in part, through the inhibition of NADPH-mediated superoxide production [14]. Moreover, **12** has been assessed in the treatment of diabetes with interesting results. Hence, **12** exhibited significant endothelial protective effect in animal models of hypertension and diabetes mellitus. In isolated thoracic aorta of spontaneously hypertensive rats (SHRs), streptozotocin (STZ)-induced diabetic rats and db/db mice, repeated treatment with boldine significantly improved the attenuated acetylcholine (ACh)-induced endothelium-dependent relaxations. The endothelial protective role of **12** correlated with increased nitric oxide (NO) levels and reduction of vascular reactive oxygen species (ROS). Thus, the results of this study shows that boldine (**12**) may exert protective effects on the endothelium via several mechanisms including protecting NO from degradation by ROS as in oxidative stress-related diseases. This fact could support the idea of using **12** against endothelial dysfunctions associated with hypertension and diabetes mellitus by interfering with the oxidative stress [15].

On the other hand, some aporphines without hydroxyl groups and, consequently with an antioxidant activity diminished, have been able of trying of strengthen the above mentioned property with the synthetic addition of amino group and the later formation of amides.

In this sense, a series of glaucine amides from aminoacids was reported, wherein 3-aminomethylglaucine derivatives were synthesized. The new amino acid derivative from 3-

aminomethylglaucine by using peptide method (EDC/HOBt) were assessed with sinapic acid (SA) as antioxidant pattern. However, the experimental data shown a lower antioxidant activity than SA, which is according to the absence of active free radical scavenger groups either NO or OH in the framework alkaloid [16].

Nevertheless, some years ago, Fan et al. presented a patent application in which aporphine derivatives as northaliporphine (**19**), for instance, was converted into its O-methyl derivative norglaucine (**20**), which was *N*-modified in reductive conditions (Scheme 1). Using **20** or **12** as starting material, the synthesized amide derivatives (**21**, **22**), for instance, exhibit more efficient antioxidant activity in comparison with carboxy group-containing agent alone and aporphine derivative alone, and they are suitable for use in treating and/or preventing hyperglycemic disease and/or several oxidative stress related diseases [17].



Scheme 1. Synthesis of aporphine amide derivatives (**21**) and (**22**) from northaliporphine (**19**).

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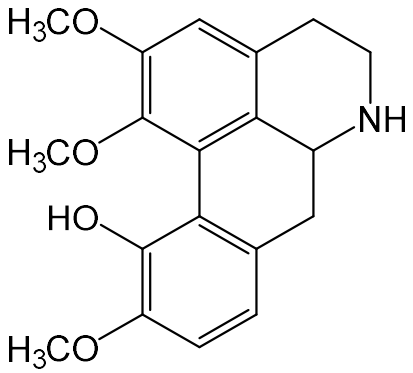
In the scope of prevent oxidative stress, adiponectin is an adipokine secreted by differentiated adipocytes, and such hormone is suggested to be correlated between oxidative stress and adiponectin levels in patients with metabolic syndrome or cardiovascular disease. Thus, an important antioxidant as boldine (**12**) and its effect on the expression of adiponectin and its regulators, CCAAT/enhancer binding protein-α (C/EBPα) and peroxisome proliferator-activated receptor (PPAR)-γ, in 3T3-L1 cells was studied. Differentiated 3T3-L1 adipocytes were exposed

to either hydrogen peroxide (H_2O_2) (100 μM) or tumor necrosis factor-α (TNFα) (1 ng/mL) for 24 h in the presence or absence of increasing concentrations of boldine (5-100 μM). Therefore, the experimental data shown that **12** is able to modulate the expression of adiponectin and its regulators in 3T3-L1 cells and has the potential to be beneficial in obesity-related cardiovascular disease [18].

Other properties that can be discover in the antioxidant alkaloids are therapeutic applications as antinociceptive. Hence, from extract of *Lindera angustifolia* Chen, folk medicine used for the treatment of contusions-induced swelling among other, were isolated several aporphines as boldine (**12**), norboldine (**13**) and norisocorydine (**23**) in order to assess the antinociceptive and free radical scavenging properties (Figure 5).



(23)

Figure 5. Chemical structure of norisocorydine (**23**).

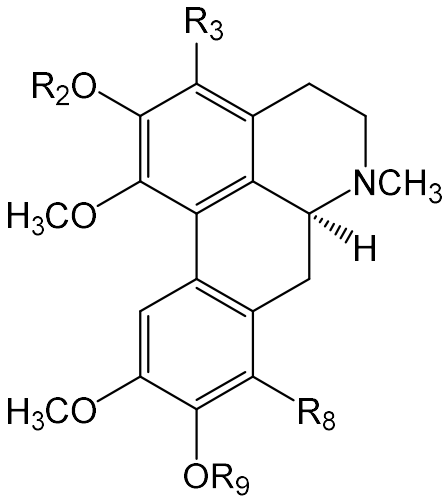
In this sense, all alkaloids exhibited remarkable radical scavenging effects (36-90% scavenging at 25-100 μg/mL) in DPPH radical scavenging test, among them **23** showed the highest activity (SC_{50}: 14.1 μg/mL). Antinociceptive activities were tested by using acetic acid-induced writhing and formalin test at dose of 20 mg/kg. **23** exhibited the highest antinociceptive ability with

83.5% writhing inhibition. **12** and **13** showed significant antinociceptive activity with 76.3% and 74.6% writhing inhibition respectively. As summary the authors of this research mention that the alkaloids from *Lindera angustifolia* possess both free radical scavenging and antinociceptive activities, and the antinociceptive activity seems to be related to the free radical scavenging effect [19].

An interesting property that some aporphines have is to act as dopamine (DA) antagonists from *in vivo* experiments, which might be useful in the treatment of some mental disorders.

Thus, boldine (**12**) that displaying antioxidative and dopaminergic properties, and six of its derivatives as glaucine (**24**), 3-bromoboldine (**25**), 3-iodoboldine (**26**), 8-aminoboldine (**27**), 8-nitrosoboldine (**28**) and 2,9-O,O'-dipivaloylboldine (**29**) were tested for these properties in comparison with their parent compound (Figure 6). Boldine derivatives (**25-28**) had been synthesized previously in order to extend the boldine alkaloid framework and to assess the antioxidant property [20, 21]. Thus, all the tested alkaloids displayed *in vitro* antioxidative properties equal to or slightly weaker than those of boldine, and equal to or stronger than (±)-6-hydroxy-2,5,7,8,-tetramethylchromane-2-carboxylic acid (Trolox). Among these aporphine derivatives, only **25** was able to reduce the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a well know neuronal dopaminergic toxin, -induced decrease of striatal levels of DA and 3,4-dihydroxyphenylacetic acid (DOPAC). Indeed, when tested on DA metabolism in the striatum of B6CBA mice, all the alkaloids, except **27**, increased striatal levels of DOPAC and homovanillic acid (HVA), and the HVA/DA ratio, indicating that they cross the blood-brain barrier and that they seem to act as dopamine antagonists *in vivo* [22]. Therefore, the authors suggest that the potent *in vitro* antioxidative property and the ability to cross the blood-brain barrier are not sufficient criteria to predict the inhibition of neuronal degeneration induced by

MPTP. These results could be considered as alternative medical option in the treatment of certain mental disorders such schizophrenia or bipolar disorder.

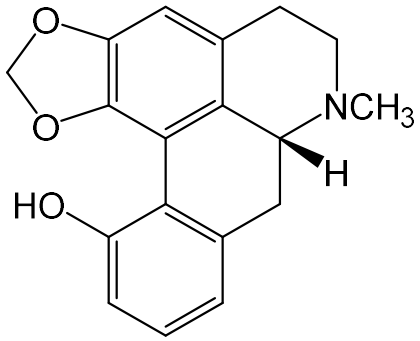


(24); $R_2 = CH_3$, $R_3 = R_8 = H$, $R_9 = CH_3$
(25); $R_2 = R_8 = R_9 = H$, $R_3 = Br$
(26); $R_2 = R_8 = R_9 = H$, $R_3 = I$
(27); $R_2 = R_3 = R_9 = H$, $R_8 = NH_2$
(28); $R_2 = R_3 = R_9 = H$, $R_8 = NO$
(29); $R_2 = COC(CH_3)_3$, $R_3 = R_8 = H$, $R_9 = COC(CH_3)_3$

Figure 6. Chemical structures of aporphine derivatives (**24-29**) from boldine (**12**).

Finally it is noteworthy to highlight the influence of these aporphine alkaloids during decades in the scope of the antioxidant application in foods and drugs as an interesting therapeutic alternative. Thereafter many studies using aporphines in treatment of mental or motor dysfunctions have been carried out with surprising experimental data to be considered as possible pharmacological drugs.

Although there are not enough examples using aporphines, the dopaminergic and antioxidant properties of pukateine (PUK, **30**), a natural aporphine derivative, was analyzed in the rat central nervous system (Figure 7).



(30)

Figure 7. Chemical structure of pukateine (PUK, **30**).

In this sense, at dopamine (DA) D_1 ([^{3}H]-SCH 23390) and D_2 ([^{3}H]-raclopride) binding sites, PUK showed IC_{50} values in the submicromolar range (0.4 and 0.6 μM, respectively). *In vitro* experiments with a crude rat brain mitochondrial suspension showed that PUK did not affect monoamine oxidase (MAO) activities, at concentrations as high as 100 μM. PUK potently (IC_{50} = 15 μM) and dose-dependently inhibited the basal lipid peroxidation of a rat brain membrane preparation. Thus, PUK showed a unique profile of action, comprising an increase in extracellular DA, an agonist-like interaction with DA receptors, and antioxidant activity [23]. This interesting property of **30** could be used in the future treatment in the Parkinson`s disease without side effects and possibly of long-action in the patient.

CONCLUSION AND RECOMMENDATION

In the scope of the antioxidants in nature, it has been clear to observe that the alkaloids are the most current active compound of many medicaments and have high relevancy in the modern medicine. For many years, the alkaloids have been used for the treatment of cancer, and other of psychiatric or motor pathway dysfunctions in the central nervous system (CNS). Nevertheless, the use of compounds that have antioxidant capacity and low side effects, is one of the reasons whereby the aporphines have been considered to be the ideal candidates, who can assemble important chemical framework characteristics for the new therapeutic drugs. The addition of OH groups that can exercise of free radical scavengers, and the possibility of formation of stable salt that avoid the oxidation or degradation of the drugs, there are important factors in the diverse experimental assays by using aporphines. The linking details of the antioxidant capacity with some pharmacological properties such as anticarcinogenic, anticinoceptive effects and for treatment, in early phase, the neurodegenerative Parkinson's disease among other, have been collected in this review. This allows us to indicate that the contribution of this group of nitrogen compounds in the development of new drugs and nutritive complements, it is of high impact in the scope of the health. Thus, research groups dedicated to the natural products have the important mission of developing new study lines and promoting the therapeutic use of these compounds in the future

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