

Naphthoquinone: Bioactivity and Green Synthesis

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Naphthoquinones are secondary metabolites isolated from different plant, bacterial, fungal and animal sources; traditionally these compounds are used for their dyeing properties, however, actually different biological activities of these compounds have been reported. In most cases, these activities are due to its ability to accept one or two electrons to form the corresponding anion or di-anion radical, which can be modulated synthetically by modifying the substituents attached to the 1,4-naphthoquinone ring, in order to enhance their therapeutic properties. At the present time, synthetic methods of these compounds should be designed according the green chemistry principles to promote more sustainable processes with low or free environmental impact. Because of this, in this chapter is described the chemistry and green synthesis of natural and synthetic naphthoquinones which can be used as potential antibacterial, antifungal, anti-parasitic and antiviral agents, as well as its mechanism of action. Contributing in the area of synthesis and screening of novel chemical compounds for antimicrobial action.

Keywords: naphthoquinone; green synthesis; antimicrobial, mechanism of action

1. Introduction

Chemical synthesis is a hot topic because of a global crisis of drug resistance, in pathogens of both clinical and agriculture importance. Many of these pathogens are resistant to multiple classes of antibiotics and is increasingly common for them to be resistant to practically all available drugs, leaving few alternatives for the treatment of infections, especially in immunocompromised patients [1,2]. Despite addition of new classes of antimicrobials, the number of currently available drugs for infections treatment remains limited. Therefore, there is a continuing need to develop new, simpler, more effective and less toxic antimicrobials agents; so naphthoquinones and derivatives are a group of great importance that has attracted interest of the scientific community.

Naphthoquinones are natural aromatic compounds that can be found in several plant families, as well as isolated of fungi, algae and bacteria. Traditionally used for their dyeing properties, however, recently a variety of biological activities of these compounds has been reported. In most cases, these pharmacological activities are related to redox and acid-base properties, which can be modulated synthetically by modifying the substituents attached to the 1, 4-naphthoquinone ring, in order to enhance their therapeutic actions. At the present time, the synthetic methods should be designed according the principles of green chemistry to promote process more sustainable with the environmental and human safe. Because of this, in this chapter is described the chemistry and green synthesis of natural and synthetic naphthoquinones as potential antibacterial, antifungal, anti-parasitic and antiviral agents, as well as its mechanism of action. Contributing in the area of synthesis and screening of novel chemical compounds for antimicrobial action.

2. Chemistry

Naphthoquinones are structurally related to naphthalene, are characterized by the presence of two carbonyl groups in the 1,4 position and 1,2 position with lower incidence, which are named as 1,4-naphthoquinones and 1,2-naphthoquinone respectively. Naturally present hydroxyl and methyl groups as substituents, can be found in free form or condensed with oligosaccharides. Naphthoquinones are highly reactive organic compounds, traditionally used as natural or synthetic dyes whose colors range from yellow to red [3,4].

In the chemistry of natural and synthetic naphthoquinones redox and acid-base properties are important because they are directly related to the biological properties possessed by different compounds. The capacity to accept one or two electrons to form the corresponding radical-anion ($Q^{\cdot-}$) and hydroquinone radical anion ($Q^{2\cdot-}$) shown in the fig. 1, can be modulated by the electro-donating and electro-withdrawing substituents attachment to naphthoquinone ring [5,6].

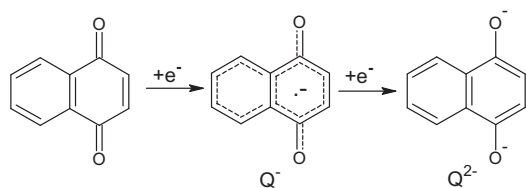


Fig. 1 Redox properties of naphthoquinone ring. Quinone produces the semiquinone radical (Q^{\bullet}) and dianion hydroquinone (Q^{2-}) by a sequence of two electron reduction.

3. Green synthesis of naphthoquinone

There are several definitions for the term green chemistry or sustainable chemistry. The United States Environmental Protection Agency (EPA) defined green chemistry as “the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances. Green chemistry applies across the life cycle of a chemical product, including its design, manufacture, use, and ultimate disposal”. This term was introduced by Paul Anastas and John Warner in the Green chemistry book [7]. One of the processes where the green chemistry philosophy can be applied is the design and synthesis of molecules, several green principles can be employed such as reduced energetic requirements, use of green solvents with poor flammability and toxicity, use of reusable catalysts, all of this, contributes to reduce separation and purification methods [8]. Recently, antibiotics and bioactive compounds have been re-designed under the principles of green chemistry and the pharmaceutical industry is more interested in green process [9].

It has been demonstrated that amino derivatives of naphthoquinone, enhanced the biological properties of this class of compounds, further, the amino-1,4-naphthoquinone moiety has been used as a synthetic key intermediate for the synthesis of several compounds [10]. There are reports describing two main ways to prepare the alkyl/arylamino naphthoquinone derivatives. The first involves a Michael 1,4-addition type reaction between the 1,4-naphthoquinone ring and the amino compound to generate 2-amino-1,4-naphthoquinone. The second involves a nucleophilic substitution by a mono- or di-halogenated derivative of 1, 4-naphthoquinone by the nucleophilic attack of the amine compound to produce the corresponding amino derivative as fig. 2 shows. However, both methods are unpractical and require tedious purifications [11].

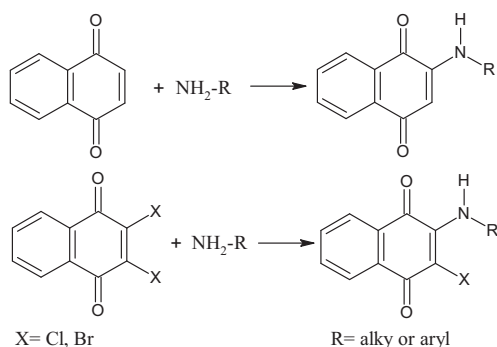


Fig. 2 Alkyl/arylamino naphthoquinone synthesis by a) Michael 1, 4-addition and b) nucleophilic substitution.

A large number of classical organic reactions can be accelerated by ultrasonic irradiation with fast reaction rate, short reaction time, high yields, and good selectivity. Ultrasound irradiation is considered an alternative source of energy compared to traditional methods and has been established as a versatile technique for synthetic chemistry. This technique relies on creation, expansion and destruction of small bubbles formed by liquid irradiation. This phenomenon is known as “acoustic cavitation”, which generates high temperatures and pressures in localized zones of a liquid creating rate acceleration in many organic reactions [12].

According to reports the ultrasound promotes the synthesis of alkyl/aryl amine naphthoquinone derivatives. For example, synthesis of new naphthoquinone derivatives with aminocarbohydrate chain in C-2 position of the quinone ring is present as a mild condition reaction between the 1,4-naphthoquinone/methoxylapachol with different aminocarbohydrates. This report showed that products are recovery in higher yields under ultrasound than using iodine as catalyst [13]. Also shown the comparison under conventional methods such as stirring at room temperature and ultrasound in the synthesis of 2-alkylamine-1,4-naphthoquinone, the yields were increase by 2- and 2.5-folds when the reaction is performed between 1,4-naphthoquinone and benzyl and hexylamine respectively; moreover, the reaction time is reduce from 7 days to 5 hours under ultrasound [14]. Another example, corresponding to the synthesis of 2-(anilino)-5-hydroxy-1,4-naphthoquinone derivatives by reaction between 5-hydroxy-1,4-naphthoquinone and anilines-substituent using the ultrasound as alternative source of activation is mentioned. The use of ultrasound promoted the

1,4-Michael addition to the naphthoquinone ring in good yields and reaction times was reduced in comparison to conventional synthesis [15].

Microwave irradiation of organic reactions has rapidly gained popularity as it accelerates a variety of synthetic transformations. Microwave enhancing procedures without use of catalyst are particularly ecofriendly. In addition this protocol has short reaction time and high yield. The synthesis of pyridylaminonaphthoquinones by reaction of 2,3-dichloro-1,4-naphthoquinone with aminopyridines is described using microwave irradiation. Results showed reduction of reaction times and improved the yields substantially comparing with conventional heating. For example, the product formed by reaction between 2,3-dichloro-1,4-naphthoquinone and *p*-amine pyridine is produced in a reaction time of 15 hours in conventional heating and 15 minutes under microwave condition [16]. The reaction of fluoroanilines and 1,4-naphthoquinone to produce novel 2-(fluoroanilino)-1,4-naphthoquinones in the presence of a Lewis acid catalyst such as $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ under mild conditions using microwave irradiation is other case of study. The reaction time was decreased from 4 hour in conventional method to a maximum of 10 minutes using the microwave method [17].

Synthesis of nitrogen 1,4-naphthoquinone derivatives in high yields under aqueous environment has been reported. Water has profound economic, environmental, safety and social advantages over conventional reactions in organic solvents leading further to the development of Green Chemistry ideology [18].

4. Biological activities

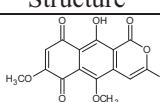
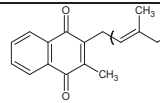
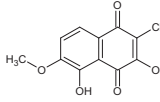
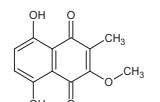
Natural and synthetic naphthoquinones derivatives are compounds that exhibit important biological activities, including antibacterial, antifungal, anti-parasitic and antiviral properties. For this reason, naphthoquinones is a group of interesting compounds of study. In this section, is present a review of compounds with potential biological activities.

4.1 Antibacterial

Antibiotics such as rifamycin, tolypomycin, damavaricin and manumycin possess the quinone ring as pharmacophore, which is part of its chemical structure. The use of naphthoquinones like antibacterial agents goes back from several decades behind: there are reports from the 60s of chemical compounds with antibacterial activity from compounds synthesized with 1,4-naphthoquinone structure [19]. In the 80s, have been studied compounds of the type 2-halo-1, 4-naphthoquinone with capability of inhibiting the growth of both Gram-positives and Gram negatives bacteria, attributing the activity to the 1,4-naphthoquinone pharmacophore and proposed this activity for inhibition of bacterial growth by working in a competitive way for the electrons transport with vitamin K [20]. Other authors have been attributed the cytotoxicity activity of naphthoquinones to inhibition of electrons transference in the mitochondrial respiratory chain, production of ROS and radical semiquinone [21, 22].

Table 1 shows to distinctive naphthoquinones isolated from medicinal plants with activity against causative bacteria of diverse infections such as *Helicobacter pylori* (chronic gastritis and peptic ulcer), *Mycobacterium tuberculosis* (tuberculosis), and *Staphylococcus aureus* (nosocomial infections). Moreover, it is showed the minimum inhibition concentration (MICs, $\mu\text{g}/\text{mL}$) of naphthoquinone and antibacterial drug used as control in the determination of antibacterial test [23-25].

Table 1 Naphthoquinones isolated from natural sources with antibacterial activity.

Compound name, source	Bacteria, MIC	Control, MIC	Structure	Ref.
5-methoxy-3,4-dehydroxanthomegnin, <i>Paepalanthus latipes</i>	<i>H. pylori</i> , 64.0 $\mu\text{g}/\text{mL}$	Metronidazole, > 254.0 $\mu\text{g}/\text{mL}$ Amoxicilin, 2.0 $\mu\text{g}/\text{mL}$		[23]
Trigonoheterona, <i>Trigonostemon heterophyllus</i>	<i>S. aureus</i> , 7.8 $\mu\text{g}/\text{mL}$	Mitomycin, 60.0 $\mu\text{g}/\text{mL}$		[24]
5-hydroxy-3,6-dimethoxy-2-methylnaphthalene-1,4-dione and 5,8-dihydroxy-3-methoxy-2-methylnaphthalene-1,4-dione, <i>Aloe secundiflora</i>	<i>M. tuberculosis</i> , 3.5 $\mu\text{g}/\text{mL}$	Rifampycin, 0.05 $\mu\text{g}/\text{mL}$	 	[25]

MIC= Minimum inhibitory concentration.

Another example of natural naphthoquinone with biological activity, is found in *Euclea natalensis* roots, which are used in the south of Africa by indigenous peoples to treat respiratory and oral diseases. From these roots, they have isolated six naphthoquinones named as diospyrin, isodiospyrin, mamegakinone, 7-methyljuglone, neodiospyrin and shinanolone. These compounds were tested against *M. tuberculosis* H37Rv getting MICs values of diospyrin (8.0 µg/mL), isodiospyrin (10.0 µg/mL), 7-methyljuglone (0.5 µg/mL) and neodiospyrin (10.0 µg/mL), the naphthoquinones performed well in comparison to some antimycobacterial drugs, such as ethambutol, isoniazid and rifampicin [26].

Knowledge of action mechanisms of compounds with naphthoquinone structure is an alternative for development of new drugs; in recent years it has been exploited the synthesis of compounds derived from natural naphthoquinones, adding different functional groups in the ring of 1, 4-naphthoquinone with MICs getting even better than many commercial drugs. Table 2 shows synthetic derivatives with antibacterial activity, MICs and drug controls used [27-32].

Table 2 Naphthoquinones synthetic with antibacterial activity.

Derivatives type	Bacteria, MIC	Control, MIC	Ref.
1,4-Naphthoquinone-[3,2-c]-1H-pyrazoles and their 1,4-naphthohydroquinone derivatives ρ -anisidilo, σ -anisidilo, phenyl and methyl	<i>Streptococcus faecalis</i> , 25.0 µg/mL <i>Klebsiella pneumoniae</i> y <i>Escherichia coli</i> , 6.2 µg/mL	Gentamycin, 0.4 µg/mL kanamycin, 16.0-32.0 µg/mL	[27]
Arylamine 123-triazole of nor- β -Lapachone	<i>Enterococcus faecalis</i> , 8.0-16.0 µg/mL	Vancomycin, 2.0 µg/mL chloramphenicol, 12.0 µg/mL	[28]
2-hydroxy-1, 4- naphthoquinone derivatives with cyane and 4-chlorophenyl moiety in C-4	<i>S. aureus</i> , 16.0-64.0 µg/mL	Ciprofloxacin and gentamicine, 0.25 µg/mL	[29]
S-, S,S-, N-, and N,S-1,4-naphthoquinone derivatives	<i>E. coli</i> , 500.0 µg/mL <i>S. aureus</i> , 62.5 µg/mL <i>Mycobacterium luteum</i> , 31.2-125.0 µg/mL	Vancomycin, ^a 14-20 mm	[30]
Amide derivatives of plumbagin, juglone, lawsone, menadione with amino acids	<i>S. aureus</i> , 3.9-125 µg/mL	Streptomycin, 3.9 µg/mL	[31]
2-ethylamino-3-methyl-1,4-naphthoquinone	<i>Pseudomonas aeruginosa</i> , 0.6 µg/mL <i>S. aureus</i> , 0.3 µg/mL	Vitamina K, 0.15	[32]

^ahalo inhibition in mm, MIC not determined.

Recently, a library of amino-1, 4-naphthoquinone-appended triazoles and triazole-chromene hybrids were synthesized and evaluated against *M. tuberculosis*. The compound 2-(((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-4-trifluoromethylphenylamino)] naphthalene-1,4-dione was the most active with a inhibition concentration to 50% (IC₅₀) of 1.87 µM better than TB-drugs as cycloserine (6 times), pyrimethamine (20 times) and equipotent as the drug ethambutol (IC₅₀<1.56 mM). These results also showed that chlorine and fluorine substitutions on aniline ring increase the antimycobacterial activity of synthesized derivatives [33].

A new series of 1, 4-naphthoquinone derivatives containing carbazole-6, 11-dione moiety was synthesized and tested against two Gram positive and six Gram negative bacteria. Compound N-{4-[4-(1,4-dioxo-1,4-dihydro-naphthalene-2-yl amino)-benzene sulfonyl]-phenyl}-3, 5-dinitro-benzamide exhibited good antibacterial activity among all the molecules studied with the best MIC of 2.1 µg/mL against *Bacillus subtilis* better than sparfloxacin that exhibited a MIC of 9.76 µg/mL. In order to understand the antibacterial activity, it was performed a molecular docking study of all the synthesized compounds with targeted *B. subtilis* proteins, the crystal structure of YmaH from *B. subtilis* were downloaded from protein data bank and different molecular docking studies were performed [34]. N and O-acetals naphthoquinone derivatives were synthesized under microwave irradiation, the most active compound against *S. aureus* with MIC of 4.0 µg/mL had the structure 2-[(ethoxymethyl)amino]-1,4-naphthoquinone [35]. In general, has been reported that compounds with 1,4-naphthoquinone structure are 8 times more active than the derivatives that have structure 1,2-naphthoquinone on the Gram positive bacteria [36, 37].

4.2 Antifungal

Fungal infections are responsible for important morbidity and mortality in humans and are mainly associated in patients immunocompromised due to organ transplant, leukemia or HIV infection [38]. This situation is enhanced by the resistance to antifungal drugs usage today, supporting the need to discover new antifungal compounds [39]. Several

reports in the literature present MICs and minimum fungicidal concentration (MFC) tests to demonstrate the antifungal potential of new compounds such as naphthoquinone.

Candida is responsible for the most infections caused by fungi and *Candida albicans* is the most important specie in fungal infections [40]. However, number of non-albicans species with important resistance or less susceptible to antifungal drugs is increasing, some of the non-albicans species with drug resistance are: *C. parapsilosis*, *C. dubliniensis*, *C. krusei*, *C. glabrata*, *C. tropicalis*, *C. guilliermondii* and *C. lusitaniae* [41]. Natural naphthoquinone have been exhibited anti-*Candida* activity. For example, 2-methoxy-1,4-naphthoquinone compound was isolated of aerial parts of *Impatiens balsamina*. This compound showed activity against *C. albicans* al-1 and al-2 with a MFCs of 0.6 and 2.5 $\mu\text{g/mL}$ respectively. Interesting, *C. albicans* CN1A and D10 strains reported with resistance to amphotericin B and fluconazole, were susceptible to 2-methoxy-1,4-naphthoquinone with MFCs of 0.6 and 1.2 $\mu\text{g/mL}$ respectively, this compound showed better *C. albicans* inhibition than the antifungal drugs (MFC, 90 $\mu\text{g/mL}$) [42]. Plumbagin exhibited an antifungal activity with MICs of 0.8 $\mu\text{g/mL}$ and MFC of 1.56 $\mu\text{g/mL}$ against *C. albicans* [43]. Shikonine showed activity against *C. krusei* with MIC 4.0 $\mu\text{g/mL}$ and *C. glabrata* with a MIC of 8.0 $\mu\text{g/mL}$, these results are comparable to those with fluconazole [44]. Lapachole has been showed antifungal activity against *C. albicans* using an *in vivo* study of *Caenorhabditis elegans* as a model organism for *Candida* infection [45].

The synthetic 3-(alkylamine)-2-chloro-1, 4-naphthoquinone (compound 3a) showed a MIC 0.2 $\mu\text{g/mL}$ [46]; and the compound 3i showed antifungal activity against *C. albicans* (ATCC 90028) using 8.0 $\mu\text{g/mL}$ [47]. Moreover, the compounds 3b and 3g inhibited *C. krusei* with MIC₉₀ of 2.4 and 2.0 $\mu\text{g/mL}$, respectively. Compound 3i with MIC of 2.0 $\mu\text{g/mL}$ for *C. parapsilosis*, 1.0 $\mu\text{g/mL}$ for *C. krusei* and 2.0 $\mu\text{g/mL}$ for *C. lusitaniae* [47].

Filamentous fungi infections are lesser frequent than *Candida* species infection, but are associated with high mortality rates. *Aspergillus* and *Fusarium* species are the most important because cause superficial, invasive and disseminated infections in humans, usually in immunocompromised patients [48]. The compound 2-methoxy-1,4-naphthoquinone was active at MLC levels against the two different fungi: *F. oxysporum* at 1.2 $\mu\text{g/mL}$ (control 90 $\mu\text{g/mL}$), *A. fumigatus* at 0.3 $\mu\text{g/mL}$ (control 1.1 $\mu\text{g/mL}$) in this study amphotericin B was used as control [42]. The synthetic derivatives 3b-3e, 3g and 3j showed activity against *A. fumigatus* with MIC₉₀ with 8.0-22.6 $\mu\text{g/mL}$. Compound 3i showed a MIC₉₀ of 4.8 and 8.0 $\mu\text{g/mL}$ against *A. flavus* and *A. fumigates*, respectively. Moreover a MIC₉₀ of 25.4 $\mu\text{g/mL}$ and 16.0 $\mu\text{g/mL}$ against *A. niger* and *F. oxysporum* respectively [47].

The fungi dermatophytes *Trichophyton rubrum* and *Trichophyton mentagrophytes* are the etiological agents in skin disease. *T. rubrum* is present over 90% of cases of onychomycosis. *T. mentagrophytes* is inhibited by eleuterine, this compound shows a lower toxicity levels than miconazole [49]. Compound 3f derivative was the most active against *T. mentagrophytes* with MIC₉₀ of 1.3 $\mu\text{g/mL}$. The most active compound for *T. rubrum* was the compound 3h with MIC₉₀ of 5.0 $\mu\text{g/mL}$ [47]. The problem with skin disease and onychomycosis are not esthetic only, because the skin problem can give rise to important complication in diabetes or peripheral vascular problems [50]. 2-methoxy-1, 4-naphthoquinone had biological activity against *T. mentagrophytes* with 1.25 $\mu\text{g/mL}$ in comparison to anfotericine B which was used as control at 90 $\mu\text{g/mL}$ [42].

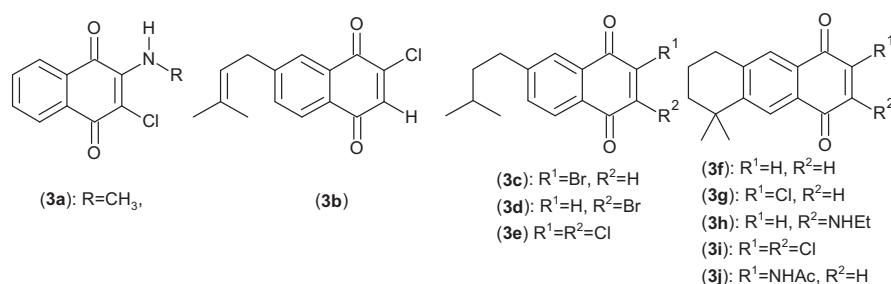


Fig. 3 Alkyl/amine 1, 4-naphthoquinone derivatives with antifungal effects.

4.3 Antiparasitic

Several research reports deal with naphthoquinones and their synthetic derivatives with a capacity to inhibit the growth of parasites such as *Toxoplasma gondii*, *Trypanosoma cruzi*, *Plasmodium falciparum*, *Schistosoma mansoni* and *Leishmania*. Leishmaniasis is a disease caused by the protozoan *Leishmania*, present in tropical and subtropical regions, and causes more than 1 million deaths per year in Africa [51]. The plumbagin and its derivative, 2-methoxy-1,4-naphthoquinone have shown activity anti-leishmania [52]. Recently, it has been demonstrated that epoxy- α -lapachone has activity against two stages morphological, promastigotes and amastigotes *in vitro* [53].

Malaria is an infection caused by a protozoan parasite of the genus *Plasmodium*, a mortal disease for a large number of people, mostly children. Within the research undertaken to eradicate this disease, 2-hydroxy-3-phenyl-1,4-naphthoquinone [54], 2-hydroxy-3-[(1-adamantil) alkyl]-1,4-naphthoquinone [55], 2-hydroxy-3-ciclohexilpropil-1,4-naphthoquinone [56], 2-alkilamino-3-chloro-1,4-naphthoquinone, and 2-amino-1,4-naphthoquinone [57] have been reported as potential antimalarial drugs around 1950's. However, it was not until 2000, when the atovacuone (2-[*trans*-

4-(4'-chlorophenyl) cyclohexyl]-3-hydroxy-1,4-naphthoquinone was introduced by Glaxo as Malarone, as a medication for malaria treatment; thus representing the greatest success in the synthesis of naphthoquinones [58]. Currently, the research has been focus on atovaquone structure, for the synthesis of new antimalarial drugs: a series of 36 new phenylsulfanylmethyl-1,4-naphthoquinones were synthesized from by a three component reaction that involves lawsone, the appropriate aldehyde and thiols with variable substitution patterns. The compounds were obtained by the underexplored epoxide-opening reaction of 1,4 -naphthoquinone using aniline derivatives such as nucleophiles [59].

S. mansoni cause the Schistosomiasis, an endemic disease, the World Health Organization (WHO) reported that 39 million people were infected by schistosomiasis throughout the world in 2012. This disease is transmitted by the mollusk *Biomphalaria glabrata*. Amino derivatives of lapachol have shown activity against *B. glabrata*, with $LC_{50} = 3.2 \mu\text{mol/mL}$ [60], other compounds with the ability to inhibit this mollusk Are 2-bromo-5-acetoxy-1,4-NQ ($LC_{50}=0.948$), 2-bromo-5-methoxy-1,4-NQ ($LC_{50}=0.746$), 3-bromo-5-acetoxy-1,4-NQ ($LC_{50}=0.893$) and the 3-bromo-5-methoxy-1,4-NQ ($LC_{50}=0.475$) [61]. Recent studies reported that plumbagina at a concentration of $10 \mu\text{M}$ promoted 100% mortality of schistosomes worms after 48 hours of treatment [62].

T. gondii is an intracellular parasite that causes toxoplasmosis, an opportunistic infection in immunocompromised individuals and human fetuses at any stage of pregnancy. The - 6- (4-methylpentyl)-2-pyrrolidine-1,4-naphthoquinone was proven *in vitro* against *T. gondii* obtaining an IC_{50} of $0.32 \mu\text{M}$ better control than when drugs like atovaquone ($IC_{50}= 16.51 \mu\text{M}$) and sulfadiazine ($IC_{50}=39.63 \mu\text{M}$) were used; also the 2-hydroxy-3- (1-prone-3-phenyl)-1,4-are reported with antiparasitic activity [63, 64]. A new pterocarpanquinone was synthesized by molecular hybridization of pterocarpano and lapachol, confirming the ability of this derivative to ensconce the parasite and growth inhibition of *T. gondii* in cell LLC-MK2 with an IC_{50} of $2.5 \mu\text{M}$ [65].

T. cruzi is the etiologic agent of American Trypanosomiasis, commonly known as Chagas disease, according to the WHO, there are 16-18 million people infected with this parasite, worldwide. Naphthoquinones and its derivatives have been synthesized and tested against the infectious form of the swallow accidentally torrent of *T. cruzi*: 2- ((8E,11Z) -heptadeca-8,11-dienyl)-3-hydroxynaphthalene-1,4-dione with a $IC_{50}=7.8 \mu\text{M}$ [66]; analogues of the β -lapachone presented a range of $IC_{50}=62.6-20.2 \mu\text{M}$ to 24 hours [67]; the synthesis of for- and ortho-naphthoquinones bearing 1,2,3-triazole substituents, as well as 1,2,3-triazoles derived from α -lapachone and nor-to-lapachone was evaluated, getting 1or derivatives with a $IC_{50/24 h}= 6.8 -50.2 \mu\text{M}$ [68]. All these derivatives showed a better activity that the drug benzimidazole $IC_{50} =103.6 \mu\text{M}$. It is reported that new oxirane derivatives of 1,4 -naphthoquinones act as agents of the tripamidas sanguine trypomastigotes of *T. cruzi* [69].

4.4 Antiviral

There are few reports about naphthoquinone as antiviral agents. There is reported that naphthoquinone derivatives have anti-HIV activity. There are a total of four targets viral proteins (envelope, reverse transcriptase, integrase and protease) and one cellular target (CCR5) for anti-HIV. In this context, it has been mentioned the synthesis of a new series of conocurvone analogues with structure of trimeric naphthoquinone and inhibition of integrase HIV-1 activity. The most active compound of conocurvone analogue showed IC_{50} at $1.50 \mu\text{M}$ [70]. Some 1,4-naphthoquinone derivatives were synthesized, and dimers of 5-hydroxy-7-methyl-1,4-naphthoquinone were isolated from *Euclea natalensis* roots (5). The HIV-1 reverse transcriptase inhibition activity of these compounds was studied *in vitro* (non-radioactive HIV-RT colorimetric assay) using the Roche Diagnostic kit and compared with that of doxorubicin as standard drug. Some of the synthesized compounds exhibited exceptionally potent (91-100%) HIV-1 RT inhibition at $100 \mu\text{g/mL}$ concentration. In this report, the most active compound was 5-hydroxy-7-methyl-1, 4-naphthoquinone with a potent inhibition of 98 % and IC_{50} $6.0 \mu\text{g/mL}$, at $50 \mu\text{g/mL}$, and 80% of inhibition even $12.5 \mu\text{g/mL}$, whereas doxorubicin shows 53% with IC_{50} 47.0 . Surprisingly the dimers showed very weak activity [71].

4.5 Mechanism

Several pharmacological activities showed by naphthoquinones and derivatives have been explicated in their redox properties. However, their actions and toxicity are still difficult to understand, at least two mechanisms have been identified: (a) their capacity to undergo redox cycling, generating reactive oxygen species (ROS), and (b) their capacity to act as electrophiles via Michael-type addition. The first one action involves a redox cycle where two electron reduction form the semiquinone radical, this reduce oxygen form superoxide anion radical ($O_2^{\cdot-}$) and thus regenerate the quinone form by cytochrome P450 reductase and another flavoprotein enzymes. $O_2^{\cdot-}$ produces oxygen radical (O_2^{\cdot}) and oxygen peroxide (H_2O_2) by enzymatic or spontaneous dismutation. O_2^{\cdot} and H_2O_2 can react together to form even more ROS such as the hydroxyl radical (OH^{\cdot}) by Fenton reaction and singlet oxygen. These ROS may react directly with biomolecules such as DNA, proteins and lipids, which leads to cell damage. In the second one, quinone form acts as electrophilic ring reacting by covalent modification of thiols or lipids, proteins, DNA and RNA [3, 32].

Atovaquone interferes in the normal process of mitochondrial chain electrons. It has been demonstrated that in *Plasmodium* species the primary active site of atovaquone action is located between the cytochrome B and c1 of complex III [72], and correspond to the electronic ac Fe-S of complex III [73].

The interaction of naphthoquinone with structural and enzymatic proteins was reported. For example, 2-methyl-1,4-naphthoquinone derivatives act as carboxylase inhibitors dependent of vitamin K, affecting the conversion of glutaryl residues of precursors proteins to γ -carboxyglutaryl [74]. The A and B isoforms of the phosphatases CDC25 are inhibited by vitamin k derivatives, affecting the activity of cellular cycle regulation in cancer cells [75]. The β -lapachone has been described as selective inhibitor and potent of re reverse transcriptase of retrovirus, decreasing the replication in humans [76]. The effect of plumbagin on microtubules, has showed that tubulin polymerization is inhibited in a doses-dependent manner, and it is proposed that compart the active site of colchicine [77].

In spite of the study of action mechanism of natural and synthetic naphthoquinone compounds is reported. This is a “hot topic” with numerous perspectives for the future, such as clinic tests, assays with several strains of the same species of microorganism, toxicological studies, synthesis of naphthoquinone derivatives with potential biological action. With it to promote the step to laboratory to commercial synthesis using methods more ecofriendly and to contribute with major of bioactive molecules with therapeutic action.

5. Conclusions

Natural and synthetic naphthoquinones are compounds with important biological activities such as antibacterial, antifungal, antiparasitic and antivirals and others. Although the naphthoquinones present high reactivity, this can be modulated to modify the atoms or groups attachment to 1,4-naphthoquinone ring. Because this, in the literature has been reported studies about the synthesis and biological activities of several molecules. Moreover, the action mechanisms and toxicological reports. However, novel molecules with potential biological effects and less secondary effects is necessary. The study of naphthoquinone and derivatives both in the area of organic synthesis, biochemistry, pharmacology, toxicology and others is important.

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