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# A REVIEW ON NAPHTHOQUINONE DERIVATIVES AS POTENTIAL ANTIMICROBIALAGENTS

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**Abstract:**

*Naphthoquinones are common phenolic substances found in nature. They are by products of secondary metabolism in high plants as well as bacterial and fungal processes. The three substances that are most common are juglone, lawsone, and plumbagin. In addition to being cytotoxic, naphthoquinones also exhibit substantial antibacterial, antifungal, antiviral, insecticidal, anti-inflammatory, and antipyretic effects. Numerous 1,4-naphthoquinones have been isolated from natural resources over the past few decades, and numerous derivatives of naphthoquinones with various structural motifs have been synthesised and tested for antimicrobial activity. Researchers are looking for new naphthoquinone derivatives with promise for clinical efficacy in an effort to find alternative effective therapeutic molecules without severe side effects..*

***Keywords:*** *Naphthoquinone, Antimicrobials*

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## INTRODUCTION:

1, 4-Naphthoquinones have antibacterial activity and are a promising new class of compound that can be used to treat bacterial infections. Bacterial infections have become the most significant threat to global human health since the Second World War, and active antibiotics have been used to cure bacterial diseases. However, the constant use of antibiotics has induced bacterial resistance, which is currently a severe problem worldwide. Therefore, the design and evaluation of active antimicrobial agents with high selectivity, less toxicity and unique novel mechanisms have become a major goal [1]. 1, 4-Naphthoquinones are widely available in many naturally occurring alkaloids and have been classified as potential antibacterial candidates [2,3]. The mechanism of these antibacterial agents involves enhanced ROS generation and is followed by apoptotic cell death [4,5]. A number of compounds with a 1,4-naphthoquinone moiety can activate noticeable biological inhibitions such as antimicrobial [6], anticancer [7], antitubercular [8], antimalarial [9] and trypanocidal [10]

activities. Due to the ability to generate ROS, naphthoquinone analogues are extremely cytotoxic to the infected cells and can restrict cellular enzymes, which are responsible for apoptosis and cell growth [11]. Consequently, these compounds have been evaluated as primary models for developing and improving clinically available antibacterial drugs. However, although the mode of action for most antibacterial drugs is known, the specific mechanism of action has not yet been elucidated.

### Recent Developments in Antimicrobial Activity

**Fernandode et al.** (2023) synthesized, and investigated the antibacterial and antitumoral activities of chemically modified CS grafted with the sodium salts of 1, 2-naphthoquinone-4- sulfonic acid or 2,3-dichloro-1,4-naphthoquinone. It was found that 1,4-NQ displayed superior antimicrobial activities against Staphylococcus aureus and Staphylococcus epidermidis associated with improved cytotoxicity and efficacy, indicated by high therapeuticindices [12]. In a study, **Liu, Z et al.** (2023) synthesized a few natural naphthoquinones and their derivatives bearing the 1,4-naphthoquinone skeleton, and their antibacterial activity against selected bacterial strains was evaluated. In vitro antibacterial activities of the compounds were investigated against Escherichia coli and Staphylococcus aureus. Under the minimum inhibitory concentration (MIC) of ≤ 0.125 μmol/L for juglone (1a), 5,8- dimethoxy-1,4-naphthoquinone (1f), and 7-methyl-5-acetoxy1,4-naphthoquinone (3c), a strong antibacterial activity against S. aureus was observed. All 1,4- naphthoquinone derivatives exhibited a strong antibacterial activity, with MIC values ranging between 15.625 and 500 μmol/L and EC50 values ranging between 10.56 and 248.42 μmol/L. Most of the synthesized compounds exhibited strong antibacterial activities against S. aureus. Among these compounds, juglone (**Fig. 1**) showed the strongest antibacterial activity [13].

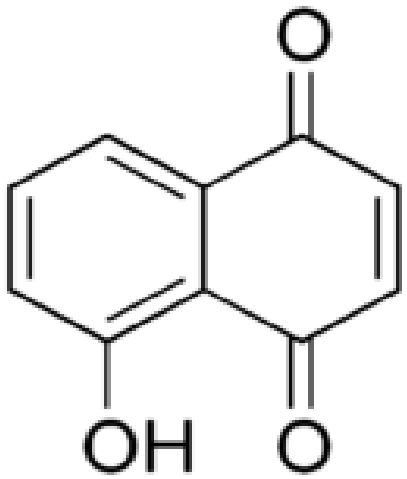


Fig. 1

Eumycetoma, the fungal form of the neglected tropical disease mycetoma, is a crippling infectious disease with low response rates to currently available antifungal drugs. In this study, a series of natural naphthoquinones and anthraquinones was evaluated for their activity against Madurella mycetomatis, which is the most common causative agent of eumycetoma. The metabolic activity of Madurella mycetomatis as well as the viability of Galleria mellonella larvae upon treatment with quinones was investigated. Several hydroxy-substituted naphthoquinones exhibited activity against Madurella mycetomatis. In particular, naphthazarin (5,8-dihydroxy-1,4-naphthoquinone) **Fig. 2** was identified as a considerably active antifungal compound against Madurella mycetomatis (IC50=1.4 μM), while it showed reduced toxicity to Galleria mellonella larvae, which is a well-established in vivo invertebrate model for mycetoma drug studies [14]

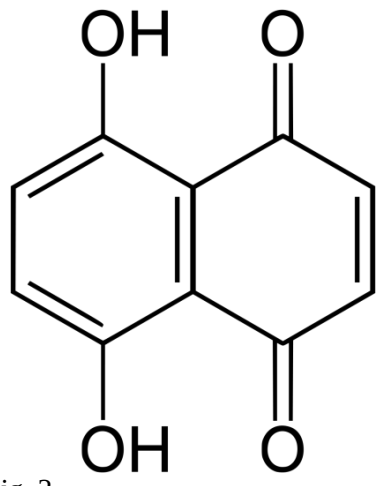


Fig. 2

The compound 3a,10b-dihydro-1H-cyclopenta[b]naphtho[2,3-d]furan-5,10-dione (IVS320) **Fig. 3** is a naphthoquinone with antifungal and antichagasic potential, but has low aqueous solubility. To increase bioavailability, inclusion complexes with -cyclodextrin (CD) and methyl--cyclodextrin (MCD) were prepared by physical mixture (PM), kneading (KN) and rotary evaporation (RE). The formation of inclusion complexes led to a change in physicochemical characteristics and a decrease in crystallinity degree. The IVS320 and IVS320-MCD/RE system exhibited anti-SARS-CoV-2 activity, showing half maximal effective concentrations (EC50) of 0.47 and 1.22 g/mL, respectively. Molecular docking simulation suggested IVS320 ability to interact with the SARS [15].

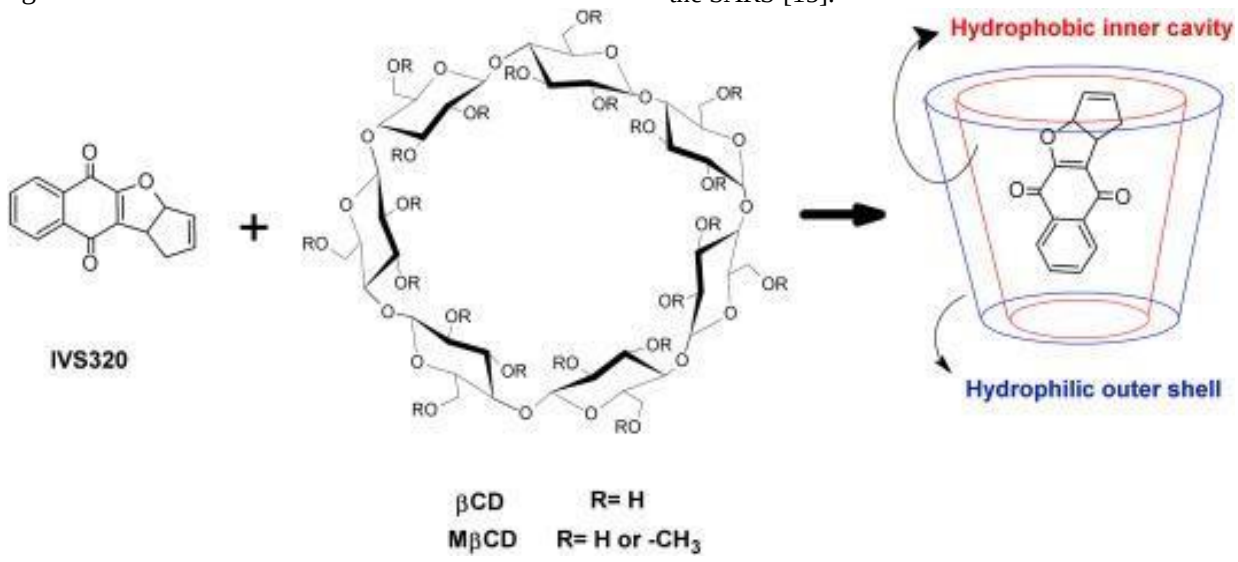


**Fig. 3**

The study presented here sought to evaluate the antimalarial activities of compounds derived from 2-amino-1,4-naphthoquinones containing 1,2,3-triazole using in vivo and in vitro models. 1H-1,2,3-Triazole 2-amino-1,4-naphthoquinone derivatives were synthesized and evaluated for antimalarial activity in vitro, using P. falciparum W2 chloroquine (CQ) resistant strain and in vivo using the murine-P. berghei ANKA strain. Acute toxicity was determined as established by the OECD (2001). Cytotoxicity was evaluated against HepG2 and Vero mammalian cell lines. Among the five compounds tested, one showed IC50 values in submicromolar range of 0.8 M. Compounds 7, 8 and 11 showed IC50 values 5 M, and selectivity index (SI) ranging from 6.8 to 343 for HepG2, and from 13.7 to 494.8 for Vero cells. Results indicated that compounds 8 and 11 may be considered hit molecules for antimalarial drug discovery platform and deserve further optimization studies [16]

This study examined the possible interactions between 1, 4-naphthoquinone and DNA. An in silico analysis indicated that 1, 4-naphthoquinone could interact with DNA through intercalation. Thermal denaturation studies revealed a change of 8°C in the melting temperature (Tm) of CT-DNA when complexed with 1, 4-naphthoquinone. The isothermal calorimetric titration (ITC) assay revealed a spontaneous intercalation between CT-DNA and 1, 4-naphthoquinone with a binding constant of 0.95 0.12 108. DNA was run through an agarose gel electrophoresis with a fixed concentration of ethidium bromide and increasing concentrations of 1,

4-naphthoquinone. The results showed that the intensity of ethidium bromide-stained DNA got reduced concomitantly with the gradual increase of 1, 4- naphthoquinone. Therefore, the results suggested that 1, 4-naphthoquinone could exhibit disintegration of the pre-existing biofilm of Staphylococcus aureus through eDNA intercalation [17]

The present study depicts the importance of altered RNA editing in various disorders and highlights ADAR2 as a potential therapeutic target. The study used molecular docking and consensus scoring to identify 47 compounds from traditional Chinese medicine that could effectively inhibit ADAR2 without causing toxicity. Molecular dynamics simulations further supported the binding of these compounds, with plausible binding free energies. One specific compound, ZINC000085511995, **Fig. 3** showed a stronger binding energy than a known binder of ADAR2. The text also mentions the potential displacement of inositol hexakisphosphate (IHP) by ZINC000085511995 in the binding site of ADAR2, suggesting a possible deactivation mechanism. Bayesian-based activity predictions supported the compounds' efficacy against neurological disorders, cancers, and viral infections. Molecular interaction analysis identified specific residues in the ADAR2 binding site, while the chemical composition of the top compounds included indole derivatives, which are associated with positive effects on mood and sleep. The compounds have potential applications in treating various disorders by targeting the ADAR2 pathway, and nine specific compounds were shortlisted as promising ADAR2 modulators [18]

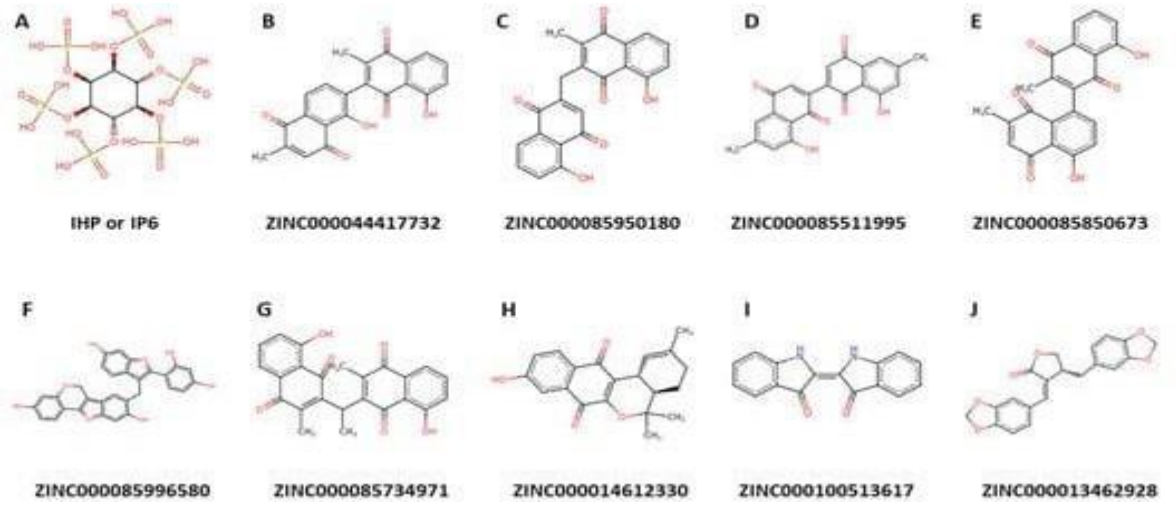


**Fig. 4**

## CONCLUSION:

Naphthoquinones have been identified as potential antimicrobial agents due to their diverse biological activities. They exhibit broad-spectrum antimicrobial properties against various microorganisms, including bacteria, fungi, and parasites. Naphthoquinones exert their antimicrobial effects through multiple mechanisms, such as disrupting cell membrane integrity, interfering with essential enzymatic processes, and generating reactive oxygen species that cause oxidative stress and damage to microbial cells. Studies have shown that naphthoquinones can effectively inhibit the growth of drug-resistant bacteria, including methicillin-resistant Staphylococcus aureus (MRSA) and multidrug-resistant strains of Mycobacterium tuberculosis. Additionally, they have demonstrated antifungal activity against pathogenic fungi, such as Candida species and Aspergillus species. The antimicrobial potential of naphthoquinones is further supported by their synergistic effects when used in combination with conventional antibiotics or antifungal agents. This combination therapy has shown enhanced efficacy in overcoming drug resistance and reducing the required dosage of existing antimicrobial drugs. Furthermore, naphthoquinones possess low cytotoxicity towards mammalian cells, making them promising candidates for the development of new antimicrobial agents with reduced side effects. However, further research is still needed to fully understand the mechanisms of action, optimize their antimicrobial activity, and evaluate their safety and efficacy in clinical settings. In conclusion, naphthoquinones exhibit promising antimicrobial properties, making them attractive candidates for the development of novel therapeutic agents against a

wide range of microbial infections, including drug-resistantstrains.

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