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β -Lapachone and Its Derivatives: Synthetic Strategies, Structure–Activity Relationships, Pharmacological Activities, and Computational Approaches

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ABSTRACT

β -Lapachone (β -Lap) is a naturally occurring ortho-naphthoquinone found in the heartwood of *Handroanthus impetiginosus* and other lapacho trees. The compound has been studied extensively due to its promising anticancer potential in cancer cells with high expression of NAD(P)H: quinone oxidoreductase 1 (NQO1). Reduction of β -Lap by NQO1 leads to the formation of a highly unstable hydroquinone intermediate which undergoes oxidation in a futile redox cycle, generating excessive amounts of ROS. The resultant oxidative stress can lead to DNA damage, hyperactivation of PARP1, reduction of NAD⁺ and ATP levels and cell death in cancer cells. Although β -Lap exhibits promising pharmacological effects, its poor solubility in water, problems with formulation and pharmacokinetics, possible toxic effects associated with dosing and limited therapeutic window limit the clinical applications of the parent compound. Therefore, various modifications of β -Lap structure were performed using the arylamino, alkoxy, thiosemicarbazone, oxime and prodrug strategies. Computer-assisted drug design approaches such as molecular docking, electronic-structure calculation and ADMET predictions serve as additional methods of selection of promising β -Lap derivatives before synthesis and testing. The present review gives a summary of the chemistry, physicochemical properties, SAR, pharmacology, synthetic and computational approaches to β -Lap and its derivatives [1-3,6].

Keywords: β -Lapachone; NQO1; Naphthoquinone; Anticancer agents; Molecular docking; ADMET

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INTRODUCTION

Cancer is a major global health issue that continues to be a principal cause of deaths. Anticancer drugs are known for poor selectivity, toxic side effects, and development of resistance. Hence, the identification of novel molecular targets for selective killing of cancer cells continues to be an important goal in medicinal chemistry [1,2,8].

Natural products continue to be a source of inspiration in anticancer drug discovery. β -Lapachone belongs to such compounds, owing to unique pharmacophore and tumor-selective action. β -Lapachone is an ortho-naphthoquinone first isolated from the heartwood of lapacho trees, which could also be produced synthetically from lapachol and other naphthoquinone precursors [1,2].

The most studied mechanism of β -Lapachone involves NQO1, the enzyme that is usually highly expressed in many solid tumors. NQO1 reduction leads to the formation of an unstable intermediate, hydroquinone, which is rapidly oxidized to generate the parent quinone along with production of ROS, thus forming a redox cycle [3]. As a consequence of the oxidative stress, DNA damage, PARP1 activation, NAD⁺ and ATP depletion and cell death are produced. β -Lapachone has been studied as a treatment for breast, pancreatic, lung, prostate and colon cancers [2,3].

Nevertheless, limited water solubility and narrow therapeutic window are the main disadvantages [1,2].

MATERIALS AND METHOD

The review was performed on published scientific papers based on β -lapachone, structural derivatives of β -lapachone, anticancer potential, molecular docking, and computational ADMET study. β -Lapachone was taken into account as the main parent compound, and structural derivatives, including arylamino, alkoxy, oxime, thiosemicarbazone, and other groups, were discussed. The computational methods, including molecular docking, were considered for the assessment of the interaction between the ligands and their targets (proteins) involved in the process of cancer development such as NQO1 and Topoisomerase II α . Binding interactions, docking score, hydrogen bonding, hydrophobic, and π - π interactions were studied according to the reported studies. Besides, the pharmacokinetic and toxicity properties were also evaluated through ADMET prediction to obtain better anticancer agents [1,4,6,7]

Structure–Activity Relationship (SAR)

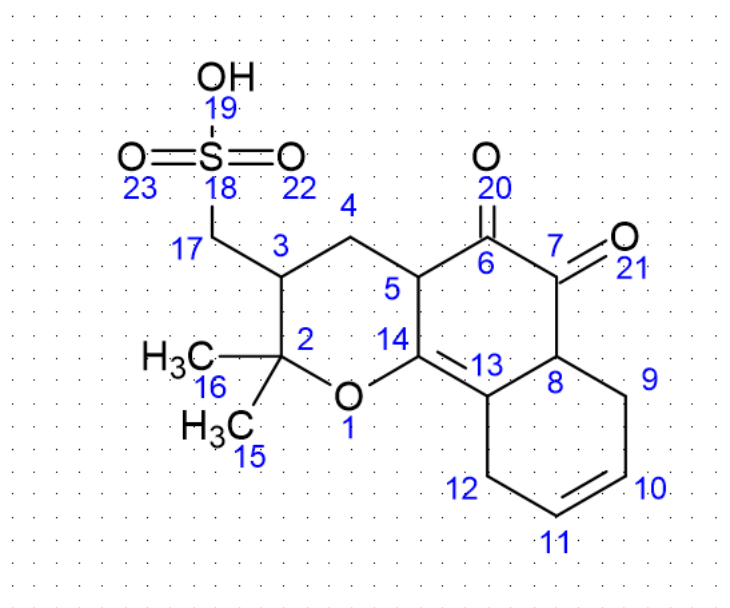


Figure 1: 2D structure of Beta lapachone -3-sulfonic acid

SAR studies are crucial in order to identify the molecular features that are responsible for β -Lapachone biological activity and to design more potent derivatives.

Importance of the quinone group

The ortho-naphthoquinone system is regarded as a critical pharmacophore, since it allows for enzymatic reduction and redox cycling, and over-modification of the quinone system could lead to a reduced ability for the desired redox process to take place [1,3].

Modification of the aromatic region

Modification of the substituents on the aromatic region can influence electron density, lipophilicity, molecular recognition, ROS generation, cellular uptake and cytotoxicity. β -Lapachone analogues containing hydroxyl and methoxy substituents have demonstrated significant anticancer activity [8].

Arylamino derivatives

3-Arylamino and 3-alkoxy-nor- β -lapachone derivatives have been synthesized and tested against several cancer cell lines, where several compounds demonstrated IC₅₀ values below 2 μ M, which suggests that appropriate substitutions can retain or improve upon anticancer activity [4].

Prodrug modification

Mono(arylimino) β -Lapachone derivatives have been developed as prodrugs, which could undergo hydrolytic conversion to β -Lapachone, improving upon pharmaceutical properties while retaining the NQO1-dependent mechanism [3].

Thiosemicarbazone derivatives

β -Lapachone-based thiosemicarbazones represent another avenue for structural-modification. Several derivatives have been synthesized and their cytotoxicity and predicted ADMET properties evaluated recently [6].

Oxime derivatives

Oxime modification has also been explored, and β -Lapachone oxime has been reported to show cytotoxicity against several cancer cell lines, with promising activity and selectivity towards NCI-H460 non-small-cell lung cancer cells, while molecular docking and pharmacokinetic prediction were used in order to investigate its potential mechanism [9].

Pharmacological Activity

NQO1-dependent anticancer mechanism

NQO1 is one of the most important biological targets associated with β -Lapachone. The proposed mechanism is that:

β -Lapachone undergoes NQO1-mediated reduction to form a hydroquinone intermediate which rapidly undergoes oxidation, regenerating β -lapachone while producing reactive oxygen species. This continuous futile redox cycle leads to an increase in oxidative stress resulting in DNA damage, PARP1 hyperactivation, NAD^+ and ATP depletion and ultimately cancer-cell death. NQO1 deficiency or inhibition can reduce cellular sensitivity to β -Lapachone, supporting the importance of NQO1 in its mechanism of action [3].

Reactive oxygen species

The continuous redox cycling of β -Lapachone can lead to the production of reactive oxygen species (ROS). Excessive ROS cause oxidative stress and damage to cellular components and is considered a major contributor to β -Lapachone-induced cancer-cell death [2].

DNA damage

β -Lapachone-induced oxidative stress leads to DNA damage. Activation of DNA-repair mechanisms, particularly activation of PARP1 leads to depletion of cellular NAD^+ and ATP, promoting cell death [3].

Topoisomerase inhibition

In addition to the NQO1-dependent mechanism, β -Lapachone has been associated with inhibition of topoisomerases and other cancer-related pathways. Topoisomerase I and II, IDO1, telomerase and Hsp90 have been investigated as additional molecular targets [1].

Anticancer activity of derivatives

β -Lapachone derivatives have shown activity against breast cancer, lung cancer, colon cancer, prostate cancer, pancreatic cancer, leukemia and melanoma. 3-Arylamino and 3-alkoxy-nor- β -

lapachone derivatives showed potent cytotoxicity against several cancer cell lines [4]. More recent studies have also demonstrated promising activity for the β -Lapachone oxime and thiosemicarbazone derivatives [6,9].

Molecular Docking and Computational Design

Molecular docking is used to predict binding interactions of β -lapachone derivatives with targets such as NQO1 and Topoisomerase II α . Binding affinity, hydrogen bonding, hydrophobic and π - π interactions are evaluated. Recent studies have combined docking with DFT, QTAIM and ADMET prediction to assess molecular interactions, pharmacokinetic properties and toxicity before biological evaluation [6,7].

RESULTS AND DISCUSSION

From the analysis of the cited studies, it becomes evident that the β -lapachone structure is promising for obtaining derivatives with anticancer activity due to its mechanism involving NQO1-mediated redox cycling and generation of ROS-induced cytotoxicity. Derivatives of β -lapachone obtained through structural modification by adding substituents to its core structure, such as arylamino, alkoxy, oxime and thiosemicarbazone groups, have shown increased or preserved anticancer activity in different cancer cell lines. It should also be noted that computational modeling techniques show the possibility of using molecular docking to determine favorable interactions between ligand and target as well as ADMET screening for predicting pharmacokinetics and toxicology of new compounds [1,4,6,7].

CONCLUSION

β -Lapachone is a promising anticancer scaffold with NQO1-mediated ROS generation as a key mechanism. However, poor solubility, pharmacokinetic limitations and toxicity restrict its therapeutic use. Structural modifications have produced derivatives with improved or altered anticancer activity. Computational approaches such as molecular docking, QSAR, DFT and ADMET prediction can support the rational design and screening of novel β -lapachone derivatives. Thus, integrating computational design, docking, ADMET evaluation, synthesis and biological testing provides a useful strategy for developing improved anticancer candidates [1,2,4,6,7].

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