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REVIEW ARTICLE

Insight into the Tubulin-Targeted Anticancer Potential of Noscapine and its Structural Analogs

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Abstract: Cancer is known as a notorious disease responsible for threatening millions of lives every year. Natural products which act by disrupting the microtubule assembly and dynamics have proven to be highly successful as anti-cancer agents but their high toxicity owing to lower selectivity has limited their usage. Recently, Noscapine (NOS), a known anti-tussive, has come out to be an effective anti-tubulin candidate with far lesser toxicity. Since its first report as an anti-mitotic agent in 1998, NOS has been extensively studied and modified by various groups of researchers to optimize its anti-tubulin activity. In this review, the recent advancements about the potential of these therapeutic candidates against various cancers have been compiled and analyzed for their inhibitory mechanism in distinct health conditions. It has been observed that the non-polar substitutions (*e.g.*, halides, aryl groups) at specific sites (9-position and N-sites of isoquinoline ring; and modification of a methoxy group) have an enhanced effect on efficacy. The mechanistic studies of NOS and its modified analogs have shown their inhibitory action primarily through interaction with microtubules dynamics thus disrupting the cell-cycle and leading to apoptosis. This review highlights the latest research in the field by providing a rich resource for the researchers to have a hands-on analysis of NOS analogs and the inhibitory action in comparison to other microtubule disrupting anti-cancer agents. The article also documents the newer investigations in studying the potential of noscapine analogs as possible anti-microbial and antiviral agents.

Keywords: Noscapine, antitubulin, antineoplastic agent, antiviral, antiprotozoal, anticancer agent.

1. INTRODUCTION

Cancer is a major health concern posing a great threat to the increasing life expectancy globally. It is regarded as a leading cause of mortality which is pacing at an alarming rate. A survey conducted in 2020 by GLOBOCAN has estimated 19.3 million fresh cases of cancer and approximately 10 million deaths in the year of survey [1]. With such aggressive pacing, cancer is believed to affect as many as 24 million people by 2035.

Early detection of cancer can shrink mortality rates but the odds of its recurrence are very high. Current treatments namely chemotherapy, radiotherapy, hormone therapy, and immunotherapy are often associated with detrimental after-effects. Multidrug resistance (MDR), adverse effects like CINV (Chemotherapy Induced Nausea and Vomiting), pain, loss of appetite, *etc*., have limited the use of currently available first and second-line drugs. Thus, researchers have been exploring alternatives, which would not only aim at killing the cancer cells without affecting the normal cells but also boost the immune response simultaneously and keep a check on the tumor cells. Some of these alternatives have come from various plant sources such as natural products like alkaloids and terpenes. One class of such molecules based on their mode of action is 'The Anti-mitotic Molecules' which kill malignant cells by interacting with the microtubule dynamics involved in the cell cycle. We have previously published reviews on the anti-cancer properties of chalcones and functionalized gold nanoparticles as gene delivery vehicles [2, 3]. In continuation to that, now we have brought another such natural product 'Noscapine' which has become an important candidate as a potential anti-cancer agent and is under trial. Noscapine, (3S)-6,7-dimethoxy-3-[(5R)-4-methoxy-6-methyl-7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-5-y1]-3H-2-benzofuran-1-one, is a naturally occurring isoquinoline opium alkaloid obtained from *Papaver somniferum* (Fig. **1**) [4]. The (-) α isomer is the naturally occurring isomer of Noscapine which involves (S, R) stereochemistry ('S' confirmation at phthalide-carbon and 'R' at isoquinoline carbon) [5]. It is a popular antitussive agent with minimal addiction. Noscapine was first reported for its anti-cancer activity by Ye *et al*. in 1998 [6]. Following this, various scientists have recognized and established it as an efficient chemotherapeutic agent due to its minimal toxicity, efficacious bioactivity, and effectiveness even in those cell lines which are resistant to many other currently available anticancer drugs [7-13]. Mechanistic studies have revealed that NOS primarily induces apoptosis through metaphase arrest in the malignant cells by binding stereo chemically to tubulin, causing the disruption of microtubule assembly dynamics and ultimately leading to "cell death".

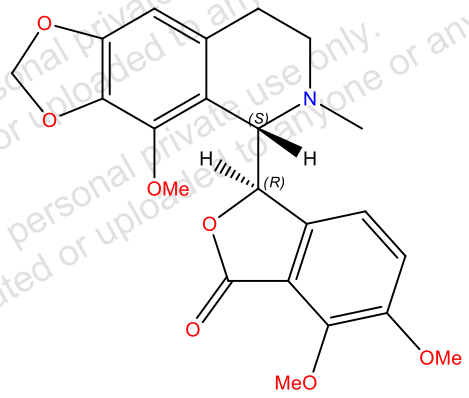

Fig. (1). Structure of Noscapine. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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