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AN EMERGING THERAPEUTIC CHEMO-PREVENTIVE PHYTOCHEMICAL NOSCAPINE EXHIBITS EFFICACY AGAINST LUNG CANCER

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ABSTRACT

The World Health Organization states that cancer is a grave public health issue that impacts millions of people worldwide and claims 9.6 million lives annually. Sadly, low- and middle-income countries are disproportionately affected by this condition. A non-toxic alkaloid noscapine, obtained from opium poppy, is widely used as cough suppressant in humans and its efficacy has been demonstrated against several cancers. Unlike other opium-derived alkaloids, oral noscapine is a safe, efficient antimitotic and antitussive drug that does not make individuals sleepy. Lung cancer is extremely fatal to life and significantly reduces a person's chances of survival. Therapy becomes increasingly difficult and inefficient since, regrettably, most lung cancer cases are not detected until the disease has advanced. A major factor contributing to treatment failure is the development of multi-drug resistance, or the cancer cells heightened resistance to numerous medications and therapies. This major obstacle in the fight against lung cancer highlights the importance of early detection and prevention actions. Noscapine is a potent chemotherapeutic agent that has garnered a lot of interest for the treatment of non-small cell lung cancer (NSCLC). Noscapine's capacity to cause apoptosis in cancer cells by manipulating several key proteins characterizes its intricate method of action. Notably, noscapine has been shown to upregulate the levels of poly (ADP-ribose) polymerase (PARP), Bcl-2-associated X protein (Bax), and caspase-3 while downregulating the expression of B-cell lymphoma 2 (Bcl-2) and increasing the Bax/Bcl-2 ratio. Additionally, noscapine exhibits antiangiogenic properties, which prevent the growth and spread of malignancies by preventing the formation of new blood vessels. These combined properties make noscapine an attractive therapy option for NSCLC and possibly against other malignancies.

KEYWORDS: Lung Cancer, Noscapine, Multi-drug resistance, Apoptosis, Anti-angiogenesis.

INTRODUCTION

Globally, cancer is the second most common cause of death after cardiovascular illnesses. According to a recent WHO study, it is estimated to have caused 10 million deaths globally in 2018—mostly in low- and middle-income countries.[1,2] Cancer is a complex disease that can be caused by a wide range of internal and environmental factors. External factors that can increase an individual's risk of cancer include regular use of tobacco products, alcohol consumption, and poor dietary choices. Meanwhile, internal factors such as hormone dysregulation and genetic changes in cell DNA may also play a significant role in the development of cancer. Approximately 20% of fatalities from cancer can be attributed to these internal sources.[3,4] Systemic medications such as hormone treatment, immunotherapy, chemotherapy, cancer vaccines, and biological therapies are used to treat metastatic tumors, whereas surgery and radiation therapy are used to treat non-metastatic malignancies.[5,6] Some studies reported that toxicity, low absorption, quick clearance, and limited metastasis are the negative effects of these therapies.[7] Chemotherapeutic agents are drugs that are used to treat rapidly dividing cells, such as cancer cells. They can be used either alone or in combination with other therapies. Nevertheless, factors including drug resistance and off-target effects limit how successful they can be.[8] The development of novel chemotherapeutic medications with enhanced selectivity, decreased toxicity, and increased efficacy is one of the primary foci of oncology research.

Lung cancer

Lung cancer is a complex disease made up of many tumors that are biologically different from one another. The two primary types of lung cancer are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC, which is further classified into three

subtypes: large cell carcinoma, squamous cell carcinoma, and adenocarcinoma, accounts for 18% of instances of lung cancer.[9] Mucus-releasing glands are the starting point for adenocarcinoma, the most common kind of non-small cell lung cancer (NSCLC). It is slightly more common in women than in men, and is more likely to be discovered near the lung's periphery. It is also more curable than other subtypes because of treatmentable mutations.[10] Squamous cell carcinoma was the most common subtype of NSCLC until the 1960s. However, since filtered cigarettes were introduced, the incidence of adenocarcinoma has increased. Deeper inhalation and higher exposure to smoke toxicants are thought to be the causes of this cancer. Adenocarcinoma is often a less serious illness, but it still requires immediate medical attention because it is still deadly.[11] It should be noted that lung cancer subtypes might present with different biological characteristics and require different treatment modalities. Therefore, receiving an accurate diagnosis and receiving the right therapy are essential to improve the prognosis and quality of life for patients with lung cancer.[12]

Noscapine as naturally occurring phytochemical

Over time, interest in natural products as a state-of-the-art in cancer treatment has grown. Consequently, researches have been done on the cytotoxic effects of the *Papaveraceae* family, which is indigenous to China, India, and Iran.[13,14] Traditional medicines have used these plants to treat various illnesses such as gastrointestinal problems, persistent coughs, and diarrhea.[46] One such naturally occurring chemical that has attracted a lot of attention recently is noscapine, an alkaloid that is a phthalide isoquinoline that is extracted from the opium poppy, *Papaver somniferum*.[15] Unlike other alkaloids produced from opium, noscapine has no sedative, addictive, or pain-relieving properties. Early in the 1960s, it was marketed as a safe cough suppressant, and patients responded favorably to it due to its low toxicity profile.[16] Nevertheless, it has recently been found to have anticancer properties due to its ability to bind with tubulin, a protein required for cell division, and stop tumor growth. Numerous investigations have demonstrated that noscapine and its analogues offer a promising path for the development of future anticancer drugs.[17,18] This is explained by its ability to preserve healthy cells while inducing autophagy, apoptosis, and cell cycle arrest in cancer cells.[19] Additionally, it has been found to inhibit angiogenesis, which slows the growth and spread of tumors by blocking the formation of new blood vessels that supply oxygen and nutrients to cancer cells.[20,21] To sum up, noscapine is a promising natural compound that may be able to combat cancer. It is a lead chemical that can be used to develop novel treatments. More research is still needed to properly explore its potential and optimize its pharmacological properties for medicinal application.

Mode of action of noscapine

Noscapine (Nos) is a naturally occurring compound that belongs to the class of benzylisoquinoline alkaloids. It is obtained from plants. It is composed of atoms of carbon, hydrogen, nitrogen, and oxygen arranged in a certain molecular configuration. $C_{22}H_{23}NO_7$ is its complicated chemical formula. The chemical is found in many plants in the families *Papaveraceae, Berberidaceae, and Ranunculaceae*, including buttercup, yellow root, and opium poppy.[22] Because of its well-known antitussive and analgesic properties, noscapine has been used for millennia in traditional medicine to treat cough, pain, and other respiratory illnesses. It is used as a medication component in several cough suppressants and other medications. Noscapine is a unique class of alkaloid; as such, it does not promote euphoria, depress the respiratory system, or create an addiction.[23] Rather, its effect on CNS activity is minimal to nonexistent. It can therefore be used as a safe and effective alternative to cough drugs such as dextromethorphan and codeine.[24,25] Noscapine has very few negative effects on humans or animals, according to some clinical studies. It has been the first-choice medicine for treating children's cough in the Netherlands for decades because of its antitussive properties. Studies have shown that noscapine may be used as an anti-inflammatory and in treating cancer, but its primary usage is as a cough suppressor.[26,27] In the past ten years, a great deal of research has been done on the pharmacological properties of noscapine, a naturally occurring alkaloid. One of the study's most significant findings is that noscapine can induce apoptosis, or programmed cell death, in cancer cell lines, which can halt the growth and spread of tumors.[28,29] Additionally, several investigations conducted both in vitro and in vivo have shown that noscapine effectively inhibits bradykinin receptors, which regulate a variety of physiological processes like blood pressure, inflammation, and pain. Based on these data, noscapine could be a viable candidate for the development of novel therapeutic strategies for cancer and related disorders.[1,30] It has been found that the structures of colchicine and noscapine derivatives are similar because they both have a dimethoxy phenyl group. It has been shown that this group behaves similarly to colchicine by acting on its receptors.[31] Interestingly, studies have shown that noscapine and its derivatives can prolong microtubule stoppage periods, which in turn reduces microtubule dynamics.[32,33] Given that microtubules are necessary for cancer cell division, this has significant implications for cancer therapy. Noscapine is believed to possess a few favorable clinical characteristics that could help it be an effective cancer treatment (Figure 1). Patients have found it to be well-tolerated because it does not cause systemic or histopathological damage. Additionally, it has good oral bioavailability and pharmacokinetics, with a roughly 10-hour clearance time.[34,35] It has also been found that noscapine has the appropriate tumor-targeting properties, which is essential to the effectiveness of any anti-cancer treatment. Taking everything into account, noscapine is a good choice for cancer treatment.

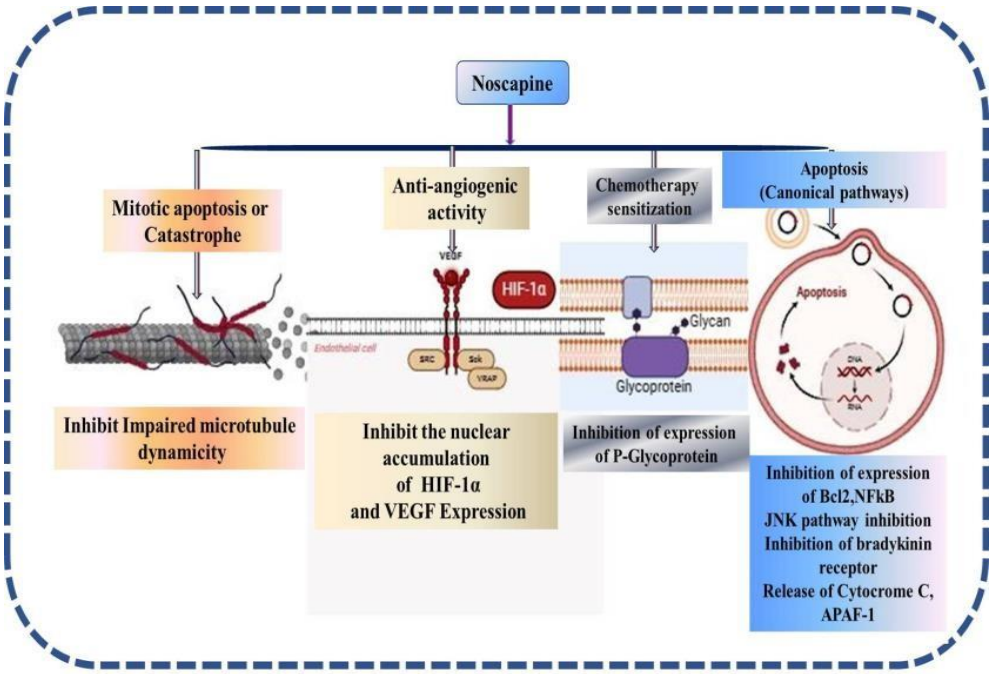

Fig. 1: Mode of action of noscapine in cancer treatment.

Anticancer molecular mechanism of noscapine with special reference to Lung cancer Noscapine exhibits various anticarcinogenic properties by regulating metastasis, inducing cell cycle arrest, and showing antimitotic propertie. It acts as a tubulin binding agent and represents anti-angiogenic properties. Non-small cell lung cancer (NSCLC) accounts for about 85% of all cases of lung cancer. Tumors are classified into three subtypes based on the types of cells observed within them: large cell carcinoma (LCC), squamous cell carcinoma (SCC), and adenocarcinoma (AC).[36,37] Because these subtypes develop in different regions of the lungs, they require different treatment techniques. Since noscapine possesses anti-cancer properties, it is a naturally occurring alkaloid that has been studied as a potential treatment for non-small cell lung cancer (NSCLC). In rat models of human non-small cell lung cancer, noscapine has been shown in preclinical experiments to inhibit cell proliferation rapidly and dose-dependently.

According to this, noscapine may be a viable therapy option for non-small cell lung cancer (NSCLC), but further research is needed to determine its efficacy and safety in human subjects.[38] The study investigated the potential of noscapine as a treatment for non-small cell lung cancer (NSCLC) using an *in vitro* and *in vivo* anti-tumor activity analysis. By upregulating PARP, Bax, and caspase-3 levels and downregulating Bcl2 expression, the results showed that noscapine effectively reduced the growth of xenografted tumors. It appears that noscapine worked by increasing the Bax/Bcl2 ratio, which in turn caused mitochondrial-mediated apoptotic processes. Additionally, the study discovered that when noscapine was given at a dose of 300 mg/kg/day, there was a non-significant increase in the Bax/Bcl2 ratio. However, a significant increase in the Bax/Bcl2 ratio was observed at noscapine dosages of 450 and 550 mg/kg/day. This suggests that noscapine may be more effective in inducing apoptosis through the mitochondrial pathway at higher dosages. Furthermore, noscapine was found to enhance caspase-3 synthesis and apoptosis in tumor xenografts, as demonstrated by strong TUNEL labeling in tumor tissues that had regressed. This suggests that noscapine may be used as a treatment for non-small cell lung cancer since it causes apoptosis via the mitochondrial system.[39]

Non-small cell lung cancer cells responded differently to 9-bromo-noscapine (9-Br-Nos) than they do to noscapine when it comes to tubulin polymerization. Researchers have developed 9-Br-Nos loaded nanostructured lipid particles (9-Br-Nos-NLPs) via the nano-emulsion method to get over the challenges associated with achieving a particle size below 100 nm. The rapid release (RR) and inhalable properties of 9-Br- Nos-RR-NLPs were then achieved by treating these particles with effervescent excipients and spray-dried lactose. In comparison to 9-Br-Nos-NLPs and 9-Br-Nos suspension, subsequent research has shown that 9-Br- Nos-RR-NLPs showed higher cytotoxicity, apoptosis, and cellular uptake in A549 lung cancer cells. These heightened effects may be due to 9-Br-Nos-RR- NLPs's increased drug transport and internalization properties, which occur through energy-dependent endocytosis and passive diffusion pathways. All things considered, the findings of this study pointed to the potential of 9-Br-Nos-RR-NLPs as an effective treatment approach for non-small cell lung cancer. The results also suggest that the unique properties of 9-Br-Nos-RR-NLPs may play a major role in the development of new cancer treatments.[40] Development of a new drug delivery mechanism for

non-small cell lung cancer therapy was the aim of the comprehensive research. By employing sterically stabilized gelatin microassemblies, the project aims to produce and characterize noscapine (SSGMS) both *in vitro* and *in vivo*. This novel medicine delivery technology was specifically targeted for human non-small cell lung cancer cells. When the cytotoxicity of SSGMS was evaluated using A549 cells, the researchers found that it had a low IC_{50} value compared to GMS and free noscapine. This suggests that the SSGMS is a more potent cancer cell-killing method. Furthermore, the progressive release of noscapine facilitated by the SSGMS contributes to a prolonged therapeutic effect. Evidence for this was the increased caspase-3 activity observed in A549 cells. All things considered, this work presented a potential way to administer medications that could improve the way non-small cell lung cancer is managed.[41] In treating NSCLC, the trial evaluated the efficacy of gemcitabine (Gem) in conjunction with noscapine (Nos). Determining the fundamental mechanism of action of combination therapy was the primary objective of the investigation. The findings demonstrated that Nos and Gem cooperated to have a favorable impact on NSCLC cells based on the IC50 values. The Nos-Gem combo treatment hampered tube formation and increased the percentage of apoptotic cells. More precisely, the combo treatment dramatically decreased the expression of cell survival proteins such as VEGF, CD31 staining, and microvessel density. Conversely, the treatment elevated the levels of fragmented DNA and cleaved caspase3. By concentrating on apoptotic and antiangiogenic processes, the research indicated that the combined therapy of Nos and Gem boosted the anticancer efficacy against lung cancer. This is significant since developing resistance to traditional chemotherapeutic medications is a major treatment challenge for non-small cell lung cancer (NSCLC). Consequently, further investigation is needed to confirm the use of Nos and Gem in combination as a viable alternative therapeutic approach for the treatment of non-small cell lung cancer (NSCLC).[42]

A recent study looked at the efficacy of treating patients with noscapine (Nos) and cisplatin (Cis) in combination, both *in vitro* and *in vivo*. The study explicitly examined the effects of this combined treatment on lung cancer cells and mouse xenograft models. The results were quite encouraging because the combination index values of the study showed that Nos and Cis had synergistic effects on the cells. In fact, this combined treatment led to the largest rise in the proportion of apoptotic NSCLC cells and elevated expression of several important proteins, including p53, p21, caspase 3, cleaved caspase 3, cleaved PARP, and Bax. Moreover, it was demonstrated that Nos and Cis inhibited the synthesis of Bcl2 and survival proteins, both of which are known to promote the development of malignancies. Nos enhanced the anticancer activity of Cis in an additive to synergistic approach by inducing many signalling pathways, including apoptosis. The combination of Nos and Cis may be a beneficial treatment choice for lung cancer patients, according to these studies, which could have a big impact on how the illness is managed.[43] Noscapine was discovered to have antiangiogenic effects on A549 cell lines in a study. VEGF levels were shown to drop at all noscapine dosages in the research.[44] The two noscapine concentrations that were most effective in reducing VEGF levels were 40 ppm and 80 ppm. The decline in VEGF levels suggests that noscapine might be a good therapeutic choice for preventing metastasis via decreasing angiogenesis. In order to determine the IC_{50} (inhibition) value, the study measured cell proliferation at various noscapine doses (10 ppm, 15 ppm, 20 ppm, 25 ppm, 30 ppm, 40 ppm, 50 ppm, 60 ppm, 65 ppm, 70 ppm, and 75 ppm) using the CCK8 cell viability assay. The study found that noscapine injection at ppm, 80 ppm, 90 ppm, 100 ppm, and at 24, 48, and 72 hours reduced cell proliferation in the A549 lung cancer cell line proportionately, depending on the dose and duration.

However, due to the potent antiproliferative effect observed at the 72-hour mark, the study was conducted within a 48-hour incubation period, utilizing previous studies as a guide. The association between noscapine and PARP in the anticarcinogenic and apoptotic actions shown in A549 cell lines is novel. According to the study, PARP levels were lower in the noscapine group than in the control group at all concentrations; the biggest difference was observed at 80 ppm noscapine concentration. The reduction in PARP levels points to the cell's apoptotic demise.[45] The purpose of the study was to determine the underlying mechanism of action and assess the effectiveness of camptothecin (CMP) and noscapine (Nos) in the treatment of non-small cell lung cancer (NSCLC). To achieve this, the researchers measured the antiproliferative effect of Nos on A549 cells and performed a cell cycle study. A fluorescence-activated cell sorting technique was used to show that the Nos+CMP treatment group had caused a G2/M phase arrest. Furthermore, there was a noticeable dose-dependent increase in the number of apoptotic cells as compared to Nos and CMP alone as well as control treatments. The scientists also carried out a Western blot analysis to determine the expression levels of several proteins in the cells. The data showed that the Nos+CMP treatment significantly raised the expression of the tumor suppressor protein p21 Waf1/Cip1, which suppresses cell cycle progression, compared to the single agent treated and control groups. Conversely, Nos+CMP expression of CDK2, an essential part of the cell machinery, and cyclin D1, a critical regulator of cell cycle progression, was significantly down-regulated compared to other groups. Additionally, Bcl2, survivin, MMP-2, and MMP-9 expression were significantly down-regulated in Nos+CMP treated cells. The researchers are currently conducting additional research to evaluate the combined anticancer effects of Nos and CMP in lung tumor xenografts in naked mice in light of these findings. The researchers discovered that Nos synergistically increased anticancer efficacy of CMP against lung cancer based on

apoptotic and cell cycle mechanisms. Thus, the findings suggest that Nos+CMP could be applied as an effective lung cancer therapy.[46]

CONCLUSION

Noscapine is an antitussive drug that has potential as an oral anticancer medication. However, its poor absorption, limited solubility, and short half-life restrict its development as a prominent anticancer drug. To overcome these limitations, novel water-soluble analogs such as 9-bromonoscapine and 9-aminonoscapine have been developed. These analogs contain a positively charged quaternary ammonium group and a negatively charged sulfonate group, improving the drug's bioavailability as an anticancer medication. Noscapine has shown a synergistic effect with other anti-tumor treatments and has the potential to treat a wide range of cancers. Although high doses can cause side effects, the usual dose of noscapine does not produce any noticeable untoward effect. In lung cancer, noscapine shows potential antineoplastic effects. It helps in apoptosis by upregulation of PARP, Bax, and caspase-3 levels and also causes downregulation of Bcl2 expression. It shows antiangiogenic properties by decreasing the expression of the cell survival proteins such as VEGF, CD31 staining, and microvessel density. Some studies show the combined treatment of noscapine with other drugs helps in cell cycle arrest in the G2/M phase. From the above studies, it can be concluded that noscapine is a potential antineoplastic agent and also has therapeutic potential against lung cancer.

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