Noscapine: An Effective Anti-Tumor Drug

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ABSTRACT

Noscapine the alkaloids naturally found in opium poppy. Noscapine contain antittusive and antitumor activity. It has microtubule binding property and potential pharmacological profile. It is clinically used because of less toxicity and excellent pharmacological profile. Noscapine can be utilized in different types of formulation in various types of cancer treatment. The major advantages and applications of noscapine are reviewed in this work.

ABBREVIATIONS

LCIS	Lobular Carcinoma In Situ
DCIS	Ductal Carcinoma In Situ
NSCLC	Non-Small Cell Lung Cancer
AC	Adenocarcinoma
SCC	Squamous Cell Carcinoma
LCC	Large Scale Carcinoma
TMZ	Temozolomide
TNBC	Triple- Negative Breast Cancer

Introduction

Noscapine is also known as narcotine and belongs to the phthalideisoquinoline alkaloids which occur naturally in opium poppy. Row opium latex contains more than 30 different alkaloids like morphine, codeine, noscapine, papaverine, thebaine, etc., of which noscapine comprises of 4 - 8 % [1]. It is synthesized from central intermediate (s)-reticuline from where morphine, codeine, and sanguinarine are also synthesized [2,3]. Noscapine is also observed in different species of the Papaveraceae and Menispermaceae.The IUPAC name of noscapine is (3S)-6,7-dimethoxy -3-[(5R)-4-methoxy-6-5methyl-7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-5-yl]-3H-2-benzofuran-1-one, its molecular formula is $C_{22}H_{23}NO_7$.

Noscapine is centrally acting as a cough suppressant and also considered as a safe and potential antitumor drug [4]. Tumor formation starts, when cells grow out of control; this happens when the molecules inside the cells misbehave [5] for example, the molecule called B-raf which normally transmit signals inside cells telling them how to behave, in some cancers notable melanoma skin cancer; B-raf is faulty and permanently switched on and commands the cells to multiply uncontrollably. To treat cancer caused by B-raf molecules researches have designed drugs to switch it off again, this can cause the cancer cells to stop growing and die. Moreover, noscapine shows little or no toxicity in the human organ [6]. Due to low toxicity and high efficacy, noscapine has an excellent pharmacological profile, neuroprotective effect [7] and is preferable in research and development of tumor-suppressive agents [8].

Pharmaceutical application of noscapine

It was first time in 1930 that the anti-tumor properties of noscapine were analyzed and since 1960 it is broadly used as a cough suppressant [9]. It is available in different forms such as tablets, lozenges or syrup as per the prescription.Noscapine has tubulin-binding property [10]. It binds tubulin in some specific ratio, changes its conformation, disrupting microtubule assembly, prevents mitosis in cells and ultimately induces cell apoptosis [11,12].

In the *in vitro* study, noscapine shows potential anti-tumor activities of various cell lines in the tumor-bearing mice and decreases mitosis of lymphonema when the drug is administered by water. It is also observed anti-tumor activities against different types of tumors such as non-small cell lung cancer, glioma, melanoma, multiple myeloma, colon, and ovarian cancer. Furthermore, it is also confirmed that noscapine does not inhibit primary immune responses, indicating that it is an efficient chemotherapeutic agent for the treatment of different types of tumors. Some of the other microtubule-binding drugs clinically used in cancer treatment, like paclitaxel, docetaxel, and vinca alkaloids [13], but due to low solubility and high toxicity, their clinical success have been limited in chemotherapy [14].

Impact on Microtubules

Microtubules are cytoskeletal structure at the time of cell division microtubules maintain genetic stability. Microtubule interference leads to programmed cell death and hence for the treatment of different tumors microtubule binding drugs are used [15]. Vincas and taxanes are clinically used microtubule drugs but they are not water soluble, results hypersensitive reaction and affect the normal dividing cells like hair follicle, bone marrow and intestinal crypt, leads to toxicity. Different from the other microtubule-targeting drugs, noscapine suppresses microtubule dynamics and even at high concentration it does not change the polymer mass of the microtubule [16]. Thus Noscapine potentially inhibits different types of tumor in animal models and culture cells without any side effect.

Anti-tumor activity of noscapine in different types of cancer

In *in vivo* and *in vitro* study researchers observed that noscapine is easily inhibited by different types of cancer with lesser or no side effects. Activity of noscapine on different type of tumor is given below:

Glioblastoma

Glioblastoma is aggressive brain cancer; glioma is a primary brain tumor that arises within the brain. It has come from one or two different types of cells in the brain. There are multiple grades of brain tumors. Grade four is the most malignant tumor called glioblastoma. It is very infiltrative and spreads into the other parts of the brain, C6 glioblastomatumor cells are implanted into the rat and orally administered the noscapine, significantly decreasing the tumor size without any toxicity [17].

Melanoma

Skin cancer is the most common cancer among all cancers; it is highly curable when detected early. Most skin cancers arise from the cell in the skin and pigment-producing cells which are commonly known as melanocytes. Melanoma begins in the melanocytes cells that produce melanin or skin color. It has been shown that noscapine remarkably inhibits melanoma progression and displays a favorable toxicity profile in the liver, spleen, duodenum, peripheral blood or bone marrow. The noscapine treatment of tumor inhibition was higher compared to paclitaxel [18]

Lymphoma

The cancer begins in white blood cells known as lymphocytes, Lymphocytes are the main part of our immune system circulated in blood vessels and lymph nodes. Noscapine repressed T-cell lymphoma in a dose-dependent manner. When noscapine is provided in the drinking water it causestumor regression. An analog, 9-nitro-noscapine treatment induces apoptosis cell death in T-cell lymphoma [20]. Another analog, EM011 treatment of mice bearing human lymphoma was effective on lymphoblastoid cells and also non-toxic to normal tissues.

Human Non-Small Cell Lung Cancer (NSCLC)

NSCLC is divided into three sub-types: adenocarcinoma (AC), squamous cell carcinoma (SCC), and large scale carcinoma (LCC). The different types of NSCLC develop in different locations of lungs. Cisplatin, gefitinib, erlotinib, gemcitabine bevacizumab, and docetaxel are drugs currently used in NSCLC. Their drug resistance and toxicity limits their potential [19]. Besides, noscapine rapidly decreases cell proliferation in human NSCLC in rats in a dose-dependent manner.

Breast Cancer

Breast cancer usually begins either where the milk is being produced, the lobules or in the milk duct. Lobular carcinoma in situ (LCIS) and Ductal carcinoma in situ (DCIS) is a precancerous condition, formed in the lobules and in the milk duct. LCIS is an invasive carcinoma while DCIS is non-invasive. It does not spread to any surrounding tissues once cancer has spread beyond the milk duct known as ductal carcinoma. Breast cancer can originate in stromal tissue - the fatty and the fibrous connective tissues of the breast. Noscapineanalog restricts the mitosis stage and causes apoptosis by binding microtubule assembly. EM011 and 9-bromonoscapine considerably retreat breast tumor implanted in nude mice [12].

Colon Cancer

Colon cancer starts out as a benign colon polyp that grows and becomes malignant over time. Colorectal cancer resists many chemotherapeutic agents. Noscapine induces apoptosis in colon adenocarcinoma cells in a p53-dependent and p21 induction [13].

Ovarian Carcinoma

Ovaries consist of 3 types of cells: epithelial, germ and stromal. When the cells in ovaries grow abnormally they develop into a cancerous cell. If a cancerous tumor is not detected early the cancer cells can spread from the ovaries throughout the pelvic region and continue to spread to the abdominal area and other organs. Noscapine is able to inhibit the mitosis stage. The study shows that the 9-nitro-noscapine prevent the cellular proliferation of ovarian cancer cells without affecting the cell cycle of normal human fibroblast cells [20].

Effect of drugs combination with noscapine

Inorder to decrease toxicity standard antimitotic drugs and increasing effectiveness of drugs, few of the studies suggest synergistic drug combinations. It shows great potential for repressing drug resistance, improving anticancer activity and declines drug-induced toxicity effects.

Table1: Combination of Drugs with noscapine and anticancer effect

Cancer	Combination with drug	Cell line	Key finding	References
Colon cancer	-	LoVo cell	Induced apoptosis via mitochondrial pathway	[21]
Lung cancer-NSCLC	Noscapine + cisplatin	A549 and H460	Combination of drugs is highly efficient for inhibiting lung	[22]

			cancer	
Brain cancer – (GBM)	Temozolomide (TMZ) resistance drug	Glioma cell line	Increased survival of animals with TMZ-resistant gliomas.	[23]
Breast cancer – (TNBC)	Noscapine + Doxorubicin	MDA-MB-231 and MDA-MB 468 cell line	Combination therapy is beneficial for aggressive TNBC	[24]
Ovarian cancer	Noscapine + cisplatin	C13K cell line	Noscapine inhibits HIF-1a and combination with cisplatin to fight ovarian cancer chemoresistance.	[25]
Lymphoma cancer	Noscapine + vincristine	CCRF-CEM and HL-60	Decrease neurotoxicity	[26]

Conclusion

Noscapine is a potential non-toxic antitumor agent and suppresses the growth of tumor in *in vitro* and *in vivo* studies. It mediates anti-proliferative, anti-invasive, proapoptotic, anti-angiogenic, and chemosensitive effects in various cancer cells. Inclusively, the review suggests that noscapine drugs have potential use for the cancer treatment.

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