The Anti-Cancer Activity of Noscapine: A Review

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Abstract: Noscapine is an isoqiunoline alkaloid found in opium latex. Unlike most other alkaloids obtained from opium latex, noscapine is not sedative and has been used as antitussive drug in various countries. Recently, it has been introduced as an anti-mitotic agent. This drug can be used orally .When the resistance to other anti-cancer drugs such as paclitaxel menifests, noscapine might be effective. Therefore, noscapine and its analogs have great potential as novel anti-cancer agents.

Keywords: Noscapine, antitussive, anti-cancer, anti-mitotic, apoptosis.

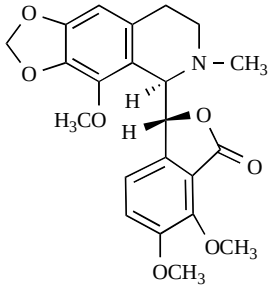
1. INTRODUCTION

Noscapine Fig. (**1**), a phthalideisoquinoline alkaloid constituting 1-10% of the alkaloid content of opium, has been used as a cough suppressant in humans and in experimental animals [1-6]. Other clinical applications of this drug are based on its anti-stroke and anti-cancer activities [7]. Some studies have shown anxiolytic effects of noscapine in mice [8]. Noscapine is a drug with low toxicity and good tolerance, as acute and chronic toxicity studies in animals shows a large margin of safety for noscapine [9]. Also, large doses of noscapine were well tolerated by 80% of the 30 cancer patients [10]. This was confirmed by B. Dahlsruom *et al.* who did not observe any side effect after 150mg oral and 66 mg intravenous administration in five healthy volunteers (4 men and 1 woman) [3].

2. PHARMACOKINETIC OF NOSCAPINE AND ITS ASSAY IN SERUM

Noscapine is rapidly absorbed after oral administration and gives a maximum plasma concentration after one hour. Its pharmacokinetics shows a bi-exponential kinetics in human healthy volunteers (either sex). Plasma concentration declines with a half-life of 13 minutes (7 to 22 minutes) for distribution and 156 minutes (range between 96-236 minutes), for elimination phases [3]. After oral administration, noscapine shows dose-dependent availability which shows extensive first-pass loss [4]. Nor-noscapine as a metabolite of noscapine has been detected in serum from all tested subjects. Nor-noscapine shows its maximal concentration at the same time as that for noscapine [4]. Values of 2.6 hours for its half-life and 4.7L/kg for volume of distribution (Vd_{area}) have been reported [3]. It has a total plasma clearance of 22ml/min/kg [3]. The absolute oral bioavialabity is found to be 30%, with a 3.6 fold inter-individual variation [3].

For evaluation of pharmacokinetic parameters of noscapine, it is required to measure its concentration in serum. Several methods have been developed for this propose [11, 12]. The lowest concentration that could be determined was 2.5 and 3ng/ml for noscapine and nor-noscapine respectively. Other noscapine metabolites, cotarnine and narcotoline could be determined at about similar concentrations, but they were not detected in the serum samples. In a recent study, pharmacokinetic studies of noscapine were performed in mice following intravenous bolus of 10 mg/kg and oral administration of 75, 150 and 300mg/kg. Oral bioavailability of noscapine was 31.5%, which offers a feasible administration of drug with precluding hypersensitivity reactions encountered drug infusion of chemotherapeutic agents [13].



Noscapine

Fig. (1). The chemical structure of noscapine.

3. BINDING STUDIES OF NOSCAPINE

Early studies using autoradiographic techniques showed that ^{3}H-noscapine binds to the brain [14]. It has been reported that dextromethorphan , an antitussive agents, binds with high-affinity and stereoselectively to the guinea-pig brain [15-17]. Other antitussive agents, such as noscapine, interact with this and enhance its binding by increasing the affinity of dextromethorphan for its central binding sites. It has been suggested that central dextromethorphan binding sites are not a subclass of opiate receptors [15, 16]. Karlsson *et al.* [18] have characterized the binding of [^{3}H] L-α-noscapine to guinea pig brain. They found that the binding of ^{3}H-noscapine to brain homogenate to be stereospecific, saturable, reversible, heat-sensitive and manifests high affinity (K_d = 7nM). Binding sites are present in all major brain areas, with the thalamus exhibiting the highest density. Subcellular localization studies showed an enrichment of

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binding sites in the synaptosomal fraction. Some structurally-related compounds with antitussive properties (narceine, hydrastine, narcotoline and papaverine) were potent competitors, while other antitussives did not inhibit ^{3}H-noscapine binding. Various ligands that bind to known neurotransmitter receptors failed to displace ^{3}H-noscapine binding or had IC_{50} values in the micromolar range. They concluded that the noscapine binding sites are different from those previously described for antitussives such as codeine and other opiates, or dextromethorphan [19, 20].

4. ANTI-CANCER ACTIVITY OF NOSCAPINE

The discovery by Joshi's team that noscapine, an alkaloid from opium, is a potent anti-tumor agent has led to considerable attention [21]. This discovery was very surprising and exciting, because noscapine has been used medicinally as a cough suppressant in humans and in experimental animals, with very few side effects and no addiction liability. In addition, its water solubility and feasibility for oral administration are valuable advantage over many other drugs for cancer therapy (for a review see ref. #19). As an anti-tumor agent, it induces apoptosis in various cell lines and arrests metaphase in dividing cells [21]. Although noscapine has chemical moieties that are similar to those of colchicine and podophyllotoxin, binding experiment and noscapine effects on the time course of colchicine binding to tubulin suggest that noscapine and colchicine bind to different site on tubulin. Superficially, noscapine shares similar chemical groups with colchicine and podophyllotoxin; however, the stereo-structure of noscapine, colchicine, and podophyllotoxin differ. Therefore, they conclude that noscapine may form other contacts on the surface of tubulin [21]. Similar group reported that the anti-mitotic activity was specific to noscapine, since closely-related compounds did not inhibit the growth of a lymphoma cell line. In addition, noscapine was shown to be effective in reducing the growth of the lymphoma and increasing the survival of tumor-bearing mice when administered in the drinking water. It is noteworthy that, noscapine showed little or no toxicity to kidney, liver, heart, bone marrow, spleen or small intestine at tumor-suppressive doses [22]. Furthermore, oral noscapine did not inhibit primary immune responses which are critically dependent upon proliferation of lymphoid cells. Thus, these results indicate that noscapine has the potential to be an effective chemotherapeutic agent for the treatment of human cancer [23].

Microtubule-binding drugs, such as paclitaxel, docetaxel, and the vinca alkaloids, are currently in clinical use for cancer chemotherapy. Unfortunately, the toxicity and low aqueous solubility have limited the applicability of these drugs in cancer chemotherapy. Moreover, their use has been hampered by the development of drug resistance contributed by multifactorial mechanisms, such as over-expression of P-glycoprotein [24], altered expression of tubulin isotypes [25], and the presence of tubulin mutations [26]. Therefore, development and/or discovery of microtubule-based compounds, such as noscapine [27] are in demand. It has been demonstrated [28] that noscapine can effectively inhibit the proliferation and induce apoptosis in both paclitaxel-sensitive and paclitaxel-resistant human ovarian carcinoma cells.

This is in agreement with the assumption that noscapine binds to tubulin at a site different from the paclitaxel-binding site, as indicated by the non-inhibitory effect of noscapine on paclitaxel binding to tubulin [28]. It has been demonstrated that the JNK pathway, via activation of the c-Jun NH2-terminal kinase (JNK), plays a role in noscapine-induced apoptosis [28].

5. ANTI-CANCER ACTIVITY OF NOSCAPINE IN VARIOUS CANCERS

Noscapine effectively inhibits the progression of various cancer types both *in vitro* and *in vivo* with no obvious side effects.

5.1. Lymphoma

Growth of T-cell lymphoma was inhibited by noscapine in a dose-dependent manner [29]. Also, noscapine can cause tumor regression when administered in the drinking water. A nitro-analog of noscapine, 9-nitro-noscapine effectively inhibits proliferation of drug-resistant lymphoblastoid cell line, with no effect on the cell cycle of normal human fibroblast cells [30]. Another noscapine analog, EM011 is also effective against vinblastine-resistant human lym-phoblastoid cells, both in cultured cells and in the mouse model. EM011 is not toxic to normal tissues at the doses effective for tumor regression [31].

5.2. Breast Cancer

It has been shown that noscapine can arrest mammalian cells at mitosis stage. Also it has potent anti-tumor activity against solid tumor when administered to mice against human breast tumor implanted in nude mice [32]. Noscapine causes apoptosis by binding to microtubule assembly, and arrests cells in mitosis. Two noscapine analog, 9-bromo-noscapine and EM011 significantly regress human breast xenograft tumor implanted in nude mice, without any detectable toxicity in tissues with frequently-dividing cells like the spleen and duodenum [32, 33]

5.3. Melanoma

Noscapine significantly inhibits melanoma progression by 83% on day 18 when delivered in drinking water. Noscapine-treated murine melanoma cells are not arrested in mitosis but rather become polyploidy followed by cell death, whereas primary melanocytes reversibly are arrested in mitosis and resume a normal cell cycle. There is no evidence of toxicity to the spleen, liver, duodenum, bone marrow, or peripheral blood. The inhibition of tumor volumes was greater after treatment with noscapine than that with paclitaxel [34].

5.4. Ovarian Carcinoma

Noscapine inhibits the proliferation of both paclitaxol-sensitive and paclitaxel-resistant human ovarian carcinoma cells [28]. Noscapine is able to arrest these human ovarian cells at mitosis. This means that noscapine might bind to tubulin at a site different from that for paclitaxol. In another study, a nitro analog of noscapine, 9-nitro-noscapine effectively inhibits cellular proliferation of ovarian cancer cells, with no effect on cell cycle of normal human fibroblast cells [30].

5.5. Glioblastoma

Noscapine significantly reduced tumor volume after oral administration to mice who had implanted rat C6 glioblastoma tumors [27], without any toxicity to the duodenum, spleen, liver or hematopoietic cells. Furthermore, noscapine treatment resulted in little toxicity to dorsal root ganglia cultures as measured by inhibition of neurite outgrowth. There was no evidence of peripheral neuropathy in animals as well. However, evidence of vasodilatation was observed in noscapine-treated brain tissue. These unique properties of noscapine, including its ability to cross the blood-brain barrier, to interfere with microtubule dynamics, to arrest tumor cell division, to reduce tumor growth, and minimally affecting other dividing tissues and peripheral nerves, warrant additional investigation of its therapeutic potential [35,36].

5.6. Colon Cancer

Although colorectal cancer is relatively resistant to many chemotherapeutic agents, noscapine induces apoptosis in a p53-dependent manner, which needs p21 induction. Therefore, noscapine can cause cell death in colon adenocarcinoma cells expressing both p53 and p21 [37].

5.7. Human Non-Small Cell Lung Cancer

Oral administration of noscapine showed significant reduction in tumor volume in human non-small cell lung tumor xenograft in nude nice in a dose-dependent manner [38].

6. INTERACTION OF NOSCAPINE WITH OTHER ANTI-CANCER DRUGS AND RADIATION

It has been shown that noscapine can efficiently inhibit the proliferation of both paclitaxel-sensitive and paclitaxel-resistant human ovarian carcinoma cells which harbor beta-tubulin mutations that impair paclitaxel-tubulin interaction [28]. Strikingly, these cells undergo apoptotic death upon noscapine treatment, accompanied by activation of c-Jun NH2-terminal kinases (JNK). Furthermore, inhibition of JNK activity by treatment with antisense oligonucleotide or transfect ion with dominant-negative JNK blocks noscapine-induced apoptosis [25].Similarly, it was also shown that noscapine could reverse the tumoral resistance and potentiate the effect of vincristine and doxorubicin in OVCAR3 cell lines [39,40]. This suggests that noscapine might be a suitable candidate as adjuvant chemo-therapeutic agent to other anti-cancer drugs.

In a recent study, noscapine enhanced the sensitivity of glioma tumor cells to radiation, resulting in a significant tumor growth delay. Given this radio-sensitizing property, noscapine might be tested in clinical trials in combination with radiotherapy [41].

7. APOPTOSIS: A MECHANISM FOR ANTI-CANCER ACTIVITY OF NOSCAPINE

The molecular mechanism responsible for the anticancer effects of noscapine is poorly understood. Several reports indicate that noscapine induces apoptosis in tumor cells [28-32, 42, 43]. In a study in our lab, the apoptotic effects of noscapine on two myeloid cell lines, apoptosis-proficient HL60 cells and apoptosis-resistant K562 cells, were analyzed [42]. An increase in the activities of caspase-2, -3, -6, -8 and -9, along with increased poly (ADP ribose) polymerase cleavage, detection of phosphatidylserine on the outer layer of the cell membrane, nucleation of chromatin, and DNA fragmentation suggested the induction of apoptosis Fig. (**2-5**). Noscapine increased the Bax/Bcl-2 ratio with a significant decrease of Bcl-2 expression accompanied with Bcl-2 phosphorylation Fig. (**6**). Using an inhibitory approach, the activation of the caspase cascade involved in the noscapine-induced apoptosis was analyzed. We observed no inhibitory effect of the caspase-8 inhibitor on caspase-9 activity. In view of these results and taking into consideration that K562 cells are Fas-null, we suggest that cas-

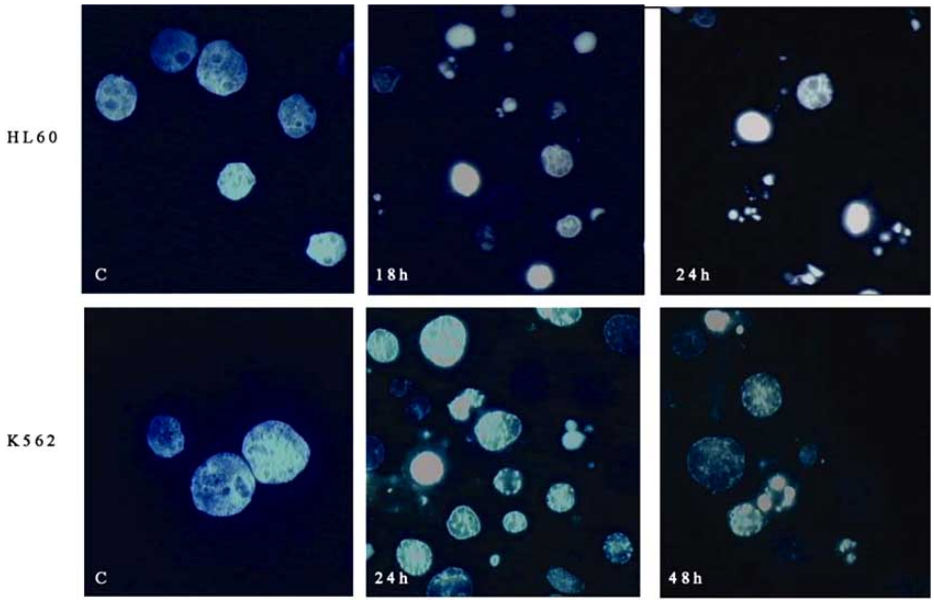

Fig. (2). Evaluation of morphological changes after noscapine administration. Cells were exposed to 20μM noscapine and examined for apoptosis by DAPI staining. Marked morphological changes, e.g., margination of chromatin, fragmented nuclei and apoptotic body appeared in time dependent manner in HL60 (A) and K562 cells (B). Magnification, ×100. Reproduced from Heidari *et al.* 2007 [42].

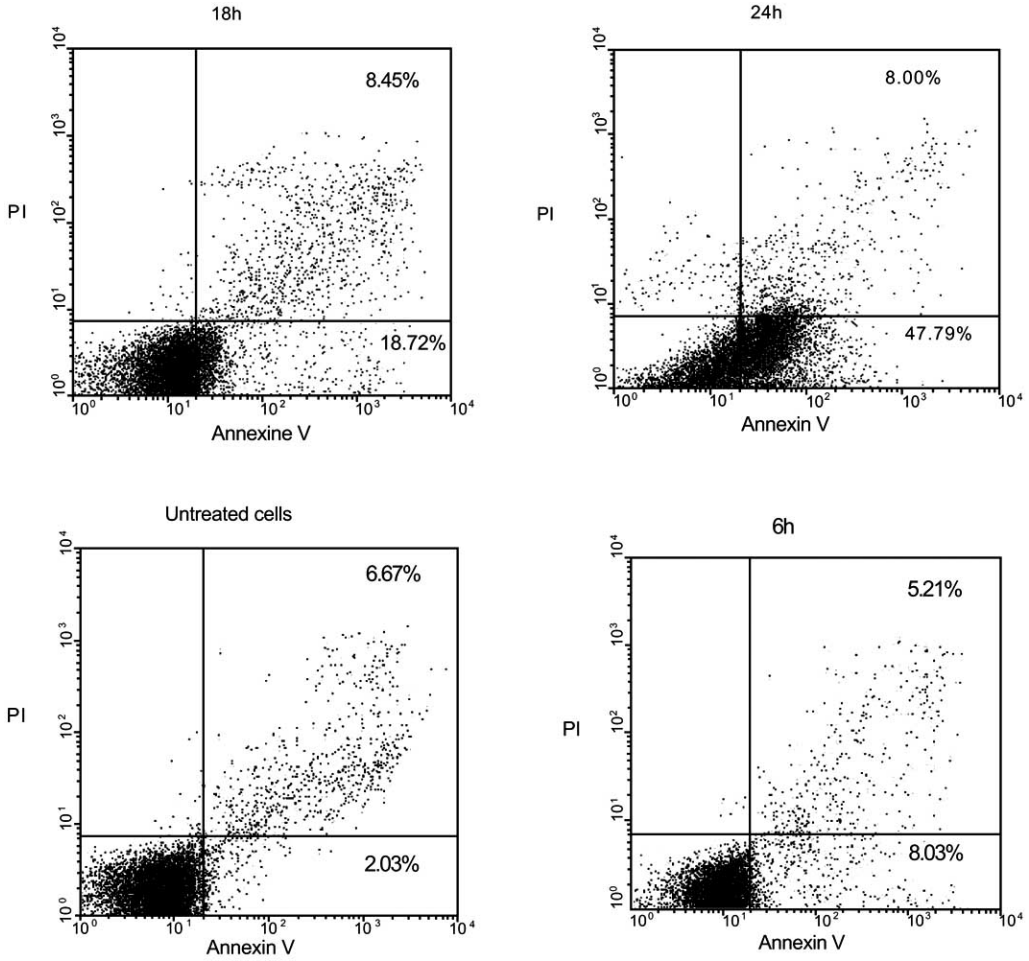

Fig. (3). Evaluation of apoptosis by annexin V positivity after noscapine administration. HL60 cells were exposed to 20μM noscapine and examined by flow cytometry after annexin V and PI staining in various times. Evidence of apoptotic cells was identified by binding of annexin V and retaining PI (lower right guardant) and double-positive cells underwent secondary necrosis (upper right quadrant). Data is a representative of three independent experiments. Reproduced from Heidari *et al*. 2007 [42].

pase-8 is activated in a Fas independent manner downstream of caspase-9. In conclusion, noscapine can induce apoptosis in both apoptosis-proficient and apoptosis-resistant leukemic cells, and it can be a novel candidate in the treatment of hematological malignancies.

In another similar study but on human glioma cells, Newcomb *et al*. [43] showed that noscapine was an inhibitor of the hypoxia-inducible factor-1 pathway in hypoxic human glioma cells and human umbilical vein endothelial cells. There, they evaluated the sensitivity of four human glioma cell lines to noscapine-induced apoptosis. Noscapine was a potent inhibitor of proliferation and inducer of apoptosis. Induction of apoptosis was associated with activation of the JNK signaling pathway concomitant with inactivation of the ERK signaling pathway and phosphorylation of the anti-apoptotic protein Bcl-2. Noscapine-induced apoptosis was associated with the release of mitochondrial protein AIF and/or cytochrome C. In some glioma cell lines, only AIF release occurred without cytochrome C release or PARP cleavage; while in others, AIF release occurred together with cytochrome C release and was associated with PARP cleavage. Their results suggest the potential importance of noscapine as a novel agent for use in patients with glioblastoma multiform due to its low toxicity profile and its potent anticancer activity.

8. MUTGENICITY EFFECT OF NOSCAPINE

There has been some concern on its possible carcinogenicity based on cell culture study [44]. However, it does not pose any hazard in low doses used as antitussive agent [11]. Similarlily, Kirpnick *et al*. [45] used yeast deletion (DEL) assay for detecting clastogens and concluded that noscapine did not lead to a significant induction of DEL, therefore is not reproducibly cytotoxic to the yeast cells.

9. ANALOGS OF NOSCAPINE

Since Antitumoral agents that affect microtubule dynamics are of great medical need, several haloderivatives of noscapine have been synthesized and evaluated for their cytotoxic activities [27]. Among these is 9-chloronoscapine whit most activity toward human glioma cell line U 87. Its easy synthesis route lends hope that it can be taken up for the development of novel anticancer drug. Similarly, 5-bromonoscapine and reduced 5-bromonoscapine showed potent microtubule-interfering agents that perturb mitosis

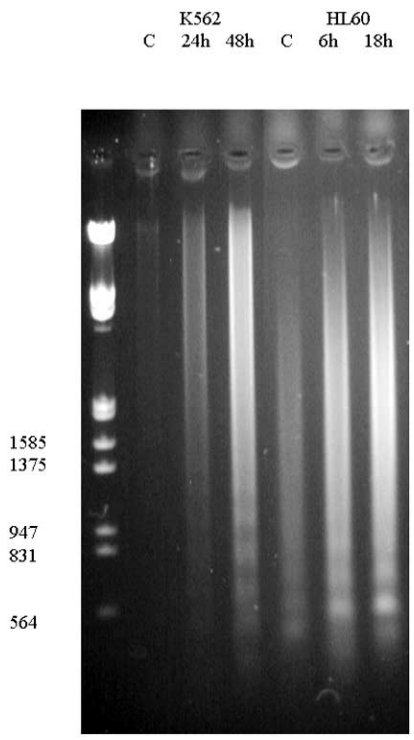

Fig. (4). Internucleosomal fragmentation of noscapine-treated K562 and HL60 cells. K562 cells were treated with 20μM noscapine for 24h and 48h and HL60 cells were treated with 20μM noscapine for 6h and 18h. After harvesting the cells, isolated DNA was analyzed by agarose gel electrophoresis. Reproduced from Heidari *et al.* 2007 [42].

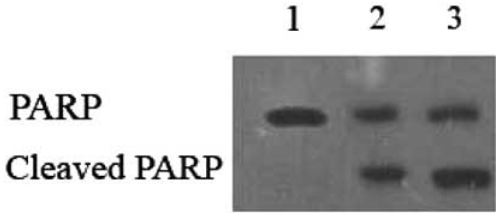

Fig. (5). Western blot assay to show cleavage of intact PARP-1(116KD) to 85 KD fragments. Lane 1, untreated cells; lane 2, 24-hours treatment by 20μM noscapine; lane3, 48-hours treatment by 20μM noscapine in K562 cells. Results are representation of three independent experiments. Reproduced from Heidari *et al.* 2007 [42].

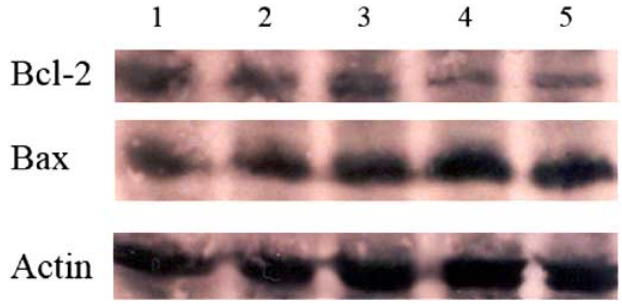

Fig. (6). Western blot analysis of Bcl-2 and Bax protein expression in K562. Lane 1, untreated cells; Lane 2, Lane 3, Lane 4, and Lane 5,cells treated with 20μM noscapine for 3 hours, 6 hours, 24 hours, and 48 hours, respectively. β-actin was used as a loading control. Reproduced from Heidari *et al.* 2007 [42].

and inhibit cell proliferation of HeLa cell line, a clone of the human ovarian carcinoma cell lines [35]. Also, a cyclic ether fluorinated noscapine analog shows potent activity, more than that of noscapine toward breast cancer cells [46]. Similarly, EM015, a 9-choloro derivative of noscapine is also binds to tubulin [27]. This analog is more active, it is orally bioavailable and has no detectable toxicity toward various tissues such as liver, kidney, spleen, lung, heart, and brain as well as neurons, which are common targets of usual anti-microtubule drugs [27].

Another analog, 9-bromonoscapine shows similar activity and induces apoptosis following G2-M arrest in hormone-insensitive human breast cancers [35]. It has been shown that 9- bromo-noscapine is 40 fold more potent than noscapine in inhibiting cellular proliferation in MCf-7 cells [47]. While, noscapine is a powerful anti-microtubule agent, it had to be said that some analogs of this compounds such as 9- nitro- noscapine has the potential to be used in the treatment of resistant cancer when other microtubule agents are ineffective.

10. RECENT PATENTS ON ANTICANCER ACTIVITY OF NOSCAPINE

Kim *et al.* patented selected compounds are effective for prophylaxis and treatment of various diseases. The invention encompasses novel compounds, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compositions and methods for prophylaxis and treatment of diseases and other maladies or conditions involving, cancer and the like. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes [48]. Welsh *et al.* also newly investigate the novel compounds which selectively bind to the delta-opioid receptor. These compounds have greater selectivity, improved water (blood) solubility, and enhanced therapeutic value as analgesics. Because agonists with selectivity for the delta-opioid receptor have shown promise in providing enhanced analgesis without the addictive properties, the compounds of the present invention are better than morphine, naltrindole (NTI), spiroindanyloxymorphone (SIOM), and other known .mu-opioid receptor selectors as analgesics [49]. Chang also patented the invention is in the field of pharmaceutical agents specifically related to compounds used and methods developed for treating cancer [50]. Kapp *et al.*, also give a patent research on noscapine derivatives comprising noscapine and its derivatives, for use in the treatment of tumors, cancer, as an adjuvant for vaccines [51].

CURRENT & FUTURE DEVELOPMENTS

It is concluded that while noscapine is an old antitussive drug, it has found new clinical applications such as use as an anti-cancer. Since, it is water-soluble and can be used orally, this drug and its analogs has great potential as an anti-cancer agent.

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